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Palladium-Catalyzed Remote *ortho*-C-H Alkenylation of Alkyl Aryl Sulfones: Access to Densely Functionalized Indane Derivatives

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Dedicated to Prof. José L. García Ruano on the occasion of his retirement.

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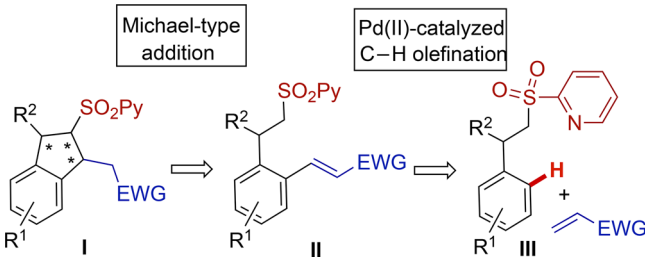
Abstract: A practical method for the palladium-catalyzed *ortho*-olefination of benzyl and phenethyl 2-pyridyl sulfones with electron-deficient alkenes using *N*-fluoro-2,4,6-trimethylpyridinium triflate ([F^+]) as the terminal oxidant is described. The chelating auxiliary (2-pyridyl)sulfonyl unit was demonstrated to be the key to the success of this reaction, which occurs efficiently with excellent regioselectivity and monosubstitution selectivity. A variety of steric and electronic changes to both coupling partners is tolerated, including substitution at the benzylic position of the sulfone compound. Furthermore, no appreciable loss of enantiopurity is observed when using non-racemic substrates. This method provides access to indane derivatives holding three contiguous stereogenic centers with high diastereocontrol. The indane framework was constructed by intramolecular Michael addition of the α-sulfonyl carbanion to the electrophilic alkene.

Keywords: C–H alkenylation; indanes; Michael-type addition; palladium; 2-pyridyl sulfones

The selective functionalization of C–H bonds is one of the most prevalent technologies for the atom- and step-economical synthesis of complex targets due to its potential to minimize the number of synthetic manipulations and reduce chemical wastes.[1] In particular, the directing group-promoted, transition metal-catalyzed oxidative coupling between arenes and olefins (Fujiwara–Moritani reaction) is a valuable tool as it enables the incorporation of a synthetically versatile alkenyl group into the product.[2] Furthermore, the use of chemically flexible directing groups provides an additional handle for the diversification of the product into architectures commonly found in natural products or medicines.[3]

For example, indane-derived compounds are valuable structural motifs present in many natural products, and biologically active molecules.[4] This versatile scaffold has also been employed in the fields of functional materials,[5] chiral auxiliaries,[6] ligands for transition metal-catalyzed reactions,[7] and organocatalysts for asymmetric transformations.[8] In connection with a project aimed at exploiting the efficiency and versatility of the (2-pyridyl)sulfonyl (SO_2Py) moiety as a directing group in C–H functionalization processes,[9] we envisioned that the densely functionalized indane skeleton **I** might be readily accessed from simple phenethyl sulfone derivatives **III** *via* a Pd(II)-catalyzed, SO_2Py-directed *ortho*-olefination followed by an intramolecular Michael-type addition of the α-sulfonyl carbanion to the newly introduced electrophilic alkene in the olefinated product **II** (Scheme 1).[10] In turn, chiral benzyl-substituted phenethyl sulfones **III**



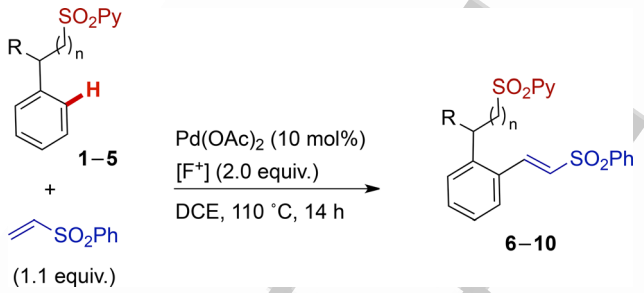
Scheme 1. Proposed access to indane derivatives.

could be easily prepared, even in an enantioselective fashion, by catalytic conjugate addition of nucleophilic reagents to α,β-unsaturated sulfones.[11]

Despite the simplicity of this approach, we anticipated several key challenges. First, although sulfur-containing functions such as sulfonamide,[9,12] sulfonate,[13] sulfoximine,[14] sulfonic acid,[15] sulfoxide[16] and sulfide[17] have recently been incorporated as directing groups in C–H functionalizations, sulfones have been scarcely explored.[18] Second, the chelation assistance is typically limited by the size of the cyclometalated intermediate, generally proceeding through a five- or six-membered ring intermediate. Instead, the C–H olefination of phenethyl sulfone **III** would represent an intriguing remote functionalization[19] of a C–H bond at the δ-position with regard to the sulfonyl group involving a seven-membered palladacycle intermediate[20] (assuming coordination to the sulfonyl oxygen) or eight-membered palladacycle species (if coordination to the pyridyl function dominates). In this regard, Zhang and co-workers have recently devised a method for the remote *ortho*-C–H alkenylation at the δ- or ε-position of benzyl, phenethyl and phenylpropyl *p*-tolyl sulfoxides in which the sulfur atom acts as the anchoring atom in the palladacycles.[16h] Third, achieving compatibility with benzylic substitution (including preservation of its stereochemical integrity) and control of the relative stereochemistry of the three contiguous stereogenic centers in **I** (four diastereomers can be formed in the cyclization step) present key challenges for the synthetic utility of this method.

For testing our proposal, we first examined the directing ability of the (2-pyridyl)sulfonyl group and how it is affected by the proximity to the target C–H bond and the presence of a benzylic substitution. For this purpose, the 2-pyridyl sulfones **1–5** were prepared and subjected to the reaction with phenyl vinyl sulfone under typical conditions previously optimized for *N*-sulfonylaniline derivatives[9c] {$Pd(OAc)_2$, (10 mol%) and *N*-fluoro-2,4,6-trimethylpyridinium triflate[21] as stoichiometric oxidant ([F^+], 2.0 equiv.) in DCE at 110 °C for 14 h; Table 1}. To our satisfaction, the parent benzyl and phenethyl derivatives **1** and **2** did participate in the alkenylation reaction in acceptable yields, although in the case of the latter lower monoolefination selectivity was observed (products **6a** and **7**, entries 1 and 2). However, the reaction falls off with the phenylpropyl sulfone **3**, holding the targeted C–H bond one position further away from the chelating atom ($n=2$, entry 3). Interestingly, consistent with the known influence of steric effects in the site selectivity of many C–H functionalizations,[22] the introduction of a substituent at the benzylic position in both substrates allowed a very high monoalkenylation reaction while improving the yield (**9** and **10**, 87% and 74%, respectively, entries 4 and 5). Remarkably, in contrast to the majority of reported C–H alkenylation reactions for which the diolefination of substrates bearing two equivalent *ortho*-C–H bonds is a persistent problem,[23] this approach allowed for facile and high yielding formation of the monoalkenylated products of benzyl and phenethyl 2-pyridyl sulfones with excellent *ortho*-regiocontrol and mono-/disubstitution selectivity using 1.1 equiv, of the alkene.[24]

Table 1. Evaluation of the directing ability of the 2-pyridyl sulfone moiety[a]

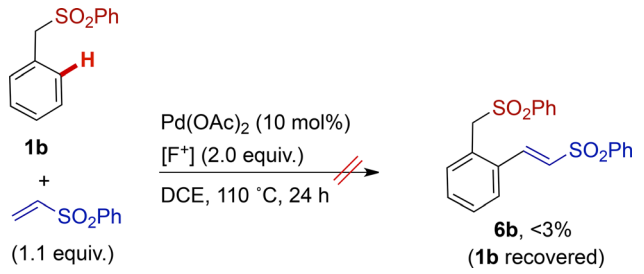


Entry	Substrate	*n*	R	Product	mono/di[b]	Yield [%][c]
1	**1a**	0	H	**6a**	95:5	67
2	**2**	1	H	**7**	81:19	41
3	**3**	2	H	**8**	–[d]	<5[d]
4	**4**	0	Et	**9**	>97:<3	87
5	**5**	1	Me	**10**	>97:<3	74

[a] *Conditions:* substrate (0.15 mmol), phenyl vinyl sulfone (0.165 mmol), $Pd(OAc)_2$ (0.015 mmol), [F^+] (0.30 mmol), DCE, 110 °C, 14 h.
[b] Determined by ^{1}H NMR.
[c] Isolated yield of the monoolefination product after purification.
[d] The starting material was recovered unaltered. [F^+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate.

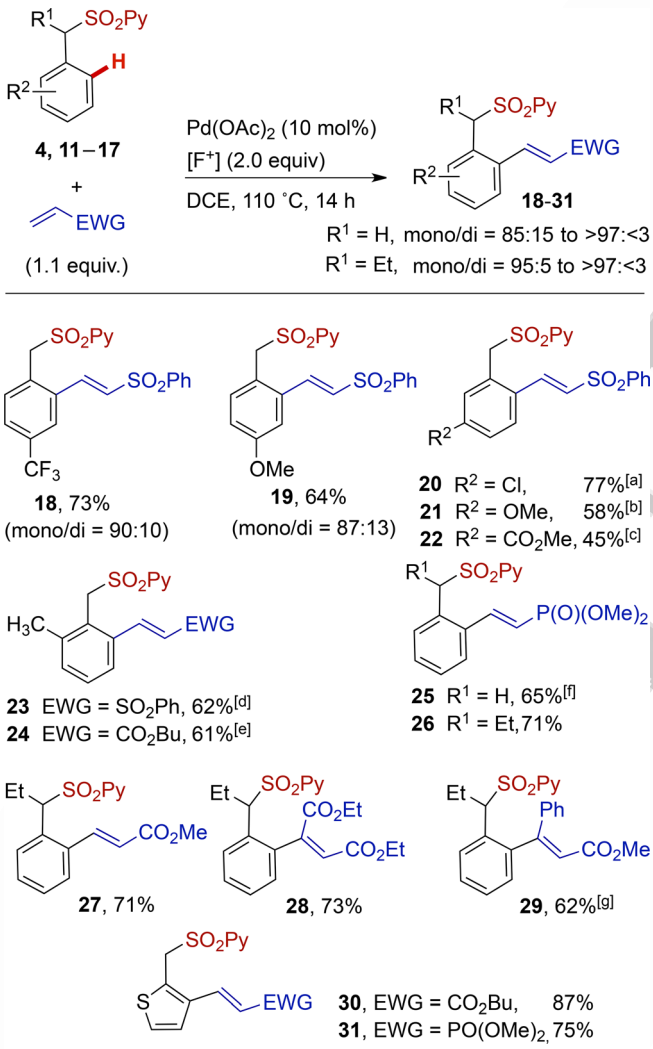
The key directing role of the (2-pyridyl)sulfonyl unit was established through a control experiment showing the complete lack of reactivity of the related benzyl phenyl sulfone (**1b**) when submitted to the reaction with phenyl vinyl sulfone under otherwise identical reaction conditions to those in Table 1, the reaction leading to exclusive recovery of starting material even after a prolonged time (Scheme 2).

An evaluation of the scope of the olefination of a variety of benzylic 2-pyridyl sulfones and electro-



Scheme 2. Control experiment with phenyl sulfone **1b**.

philic alkenes is summarized in Scheme 3. Synthetically useful yields of monoolefinated products were attained for nearly all substrates examined, regardless of the steric and the electronic properties of the arene partner (typically >60% yield). In most cases, however, a small amount of other isomers (mainly diolefinated product in substrates lacking substitution at the benzylic position) was detected in the crude mixtures. When a *meta*-substituted starting material is employed, the regioisomer with the alkene moiety being installed at the less hindered *ortho*-position is produced as the major product. For example, the *meta*-chloro sulfone **13** produced three products in a ratio

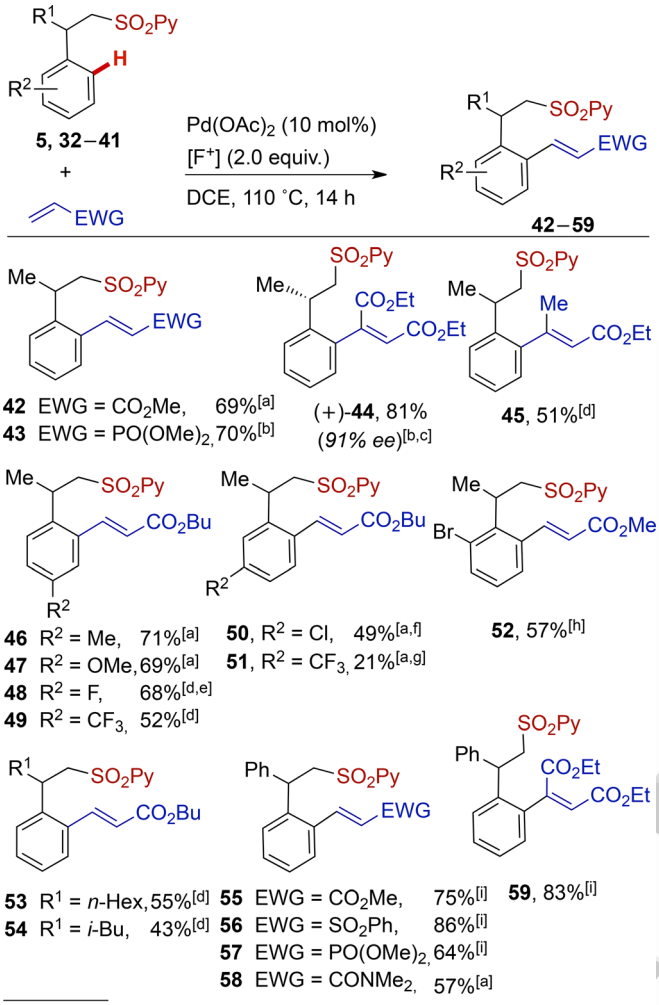


[a] Mono/mono'/di = 80:14:6.
[b] Mono/di = 88:12.
[c] 59% conversion, 95% monoselectivity.´
[d] 3 equiv. of olefin.
[e] 2 equiv. of olefin.
[f] Mono/di =90:10.
[g] 1.5 equiv. of olefin. Bu=*n*-butyl.

Scheme 3. Olefination of benzyl sulfone derivatives.

of 80:14:6 (judged by ^{1}H NMR analysis of the crude reaction mixture), of which the two main components were isolated and characterized. The major product, identified as **20** (77%), was accompanied by the alkenylation product at the most hindered *ortho'* position (**20′**, 10%, not shown), along with traces of the di-*ortho*-olefination product that could not be characterized because of its limited quantity. Nevertheless, the survival of the Cl substituent is remarkable, providing products suitable for further elaboration. The reaction of the *meta*-methoxy derivative **14**, led to an 88:12 mixture of mono-/diolefination products, where the major isomer **21** was isolated in 58% yield. On the other hand, the presence of a strongly deactivating substituent at the *meta*-position such as an ester group (substrate **15**) provided **22** in reduced yields (45%) due to incomplete conversion (59%). Meanwhile *ortho*-C–H functionalization is typically very sensitive to the steric hindrance imposed by aryl *ortho'*-substituents, leading to non-productive substrates or much lessened reactivity. In this alkenylation method, however, *ortho*-substitution does not seem to affect the outcome of the reaction, yet it resulted in reduced reactivity, requiring 3 equivalents of the alkene reactant (**23** and **24**, 61–62%). The reactions with substrates branched at the benzylic position gave generally higher monosubstitution selectivity (≥95%). The compatibility with heteroarenes, illustrated with thienyl derivatives **30** and **31**, is also noteworthy. With respect to the alkene reaction partner, not only the typical conjugated electron-deficient alkenes but also 1,2-disubstituted alkenes such as diethyl fumarate (**28**, 73%) and *E*-methyl cinnamate (**29**, 62%) proved to be efficient substrates for this transformation.

Encouraged by the good tolerance of our catalyst system towards different substitution patterns and functional groups, the scope of phenethyl sulfone derivatives as coupling partners was next evaluated (Scheme 4). The results nicely parallel those previously found with benzyl sulfone derivatives in terms of tolerance to a broad range of *para*-, *meta*-and *ortho*-substituted aryl rings with diverse steric and electronic properties, and versatility with regard to the substitution at the alkene coupling partner, yet a fine adjustment of the amount of alkene (1–3 equiv.) was needed for obtaining the optimum balance between conversion and mono-/diolefination selectivity. It is interesting to note that even a bulky *ortho*-bromo substituent was relatively well tolerated (**52**, 57%). The presence of a strongly deactivating substituent (e.g., CF_3) typically reduces the reactivity providing lower yields (products **49** and **51**), an effect that seems to be much more pronounced when the electron-withdrawing group is attached to the *meta*-position as previously observed in the benzyl sulfone series (**22** and **51**). Also worthy of mention is that the R^1 substituent at the benzylic position can range in



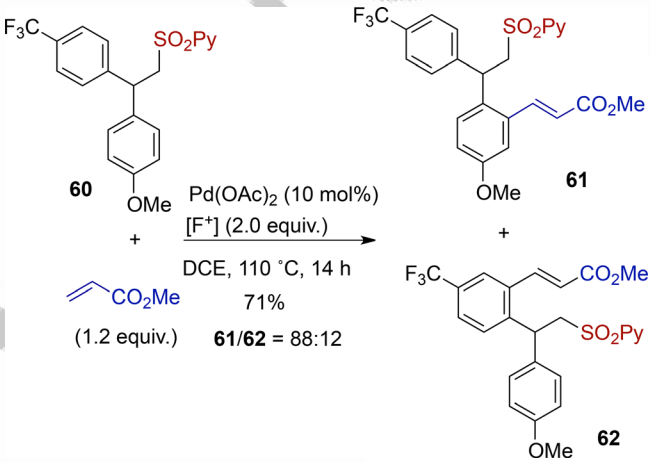
[a] 1.2 equiv. of olefin.
[b] 1.1 equiv of olefin.
[c] (+)-**5** of 91% *ee* was used as starting material.
[d] 1.5^^equiv of olefin.
[e] Methyl ester instead of *n*-butyl ester.
[f] Alkenylation product at the most hindered ortho position was also isolated in 18% yield.
[g] 33% conversion (by ^{1}H NMR).
[h] 3.0 equiv. of olefin.
[i] 1.0 equiv. of olefin. Bu = *n*-butyl.

Scheme 4. Olefination of phenethylamine derivatives.

steric demand from methyl to hexyl (**53**, 55%) and isobutyl (**54**, 43%), and it can also be aromatic (**55**–**59**, 57–86%).

We were eager to test whether this alkenylation protocol preserves the stereochemical integrity of the stereogenic center at the benzylic position when using enantiomerically enriched substrates. For that purpose, substrate (+)-**5** was prepared with 91% *ee*, following our previously reported Cu-catalyzed asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated sulfones[11h] (see the Supporting Information). Pleasingly, the reaction of (+)-**5** (91% *ee*) with diethyl fumarate took place without loss of enantiopurity, affording the corresponding olefination product (+)-**44** in 81% yield with 91% *ee* (Scheme 4).

The tolerance to aryl substituents at the benzylic position led us to question whether this catalyst system might enable the chemoselective alkenylation of a substrate having two electronically distinct aryl groups. To test the electronic bias for the olefination reaction, β,β-diaryl-substituted sulfone **60** holding an electron-deficient and an electron-releasing aromatic rings was prepared and subjected to the reaction with methyl acrylate (1.2 equiv.) under the standard reaction conditions (Scheme 5). This experiment revealed a strong preference for the electron-rich *p*-methoxyphenyl group (**61**/**62** = 88:12).

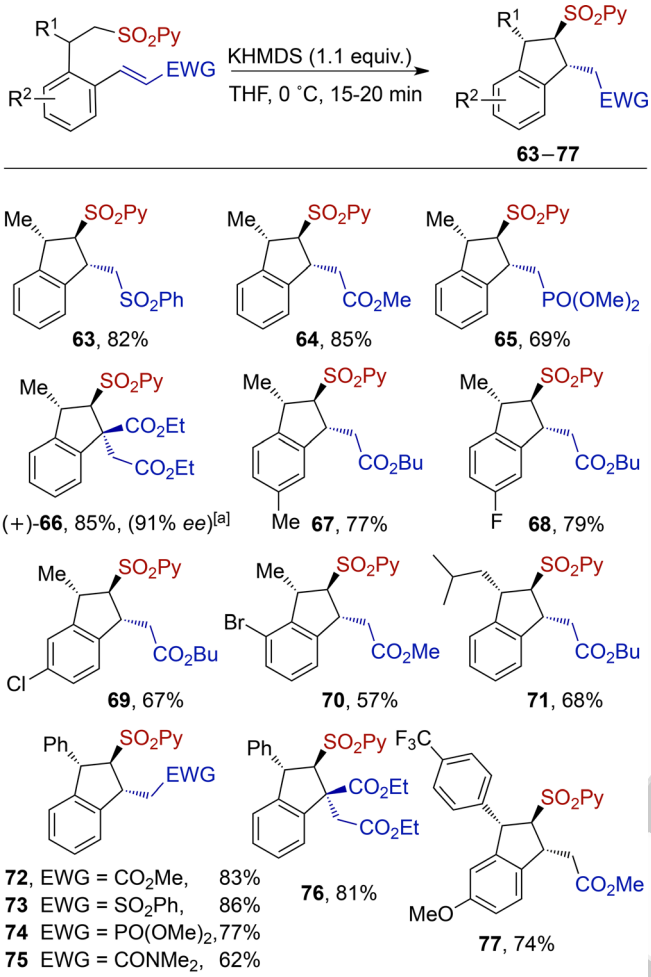


Scheme 5. Evaluation of the electronic bias for the olefination reaction.

In accordance with our desired goal of developing a method to access indane derivatives, we secured conditions for the efficient cyclization of the alkenylation products. Simple treatment of a solution of the products shown in Scheme 3 in THF at 0 °C with KHMDS (1.1 equiv.) enabled the rapid access to functionally dense indane derivatives with excellent control of the stereorelationship between the three contiguous stereocenters (Scheme 6). In all cases studied, a single stereoisomer of the indane derivative was detected by ^{1}H NMR. The all-*trans* relative stereochemistry pattern was confirmed by means of NMR spectroscopy (mainly by NOE experiments) and, in the case of products **66**, **70**, **76**, and **77** by single-crystal X-ray crystallography.[25]

We confirmed that this base-promoted cyclization reaction takes place with no appreciable racemization, as demonstrated in the reaction with maleate (+)-**44** (91% *ee*), which occurred with full preservation of its stereochemical integrity [product (+)-**66**, 85% yield, 91% *ee*].

Finally, our attention was shifted to the removal of the directing group in the final products. Typical liter-

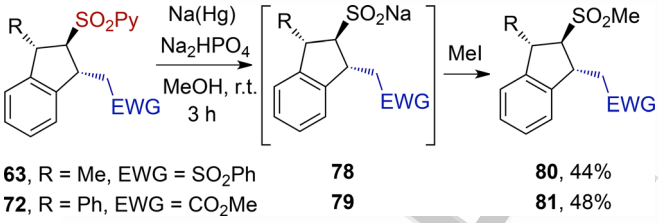


[a] A sample of (+)-**44** of 91% *ee* was used as starting material. Bu = *n*-butyl.

Scheme 6. Stereocontrolled access to indane derivatives with three contiguous stereocenters.

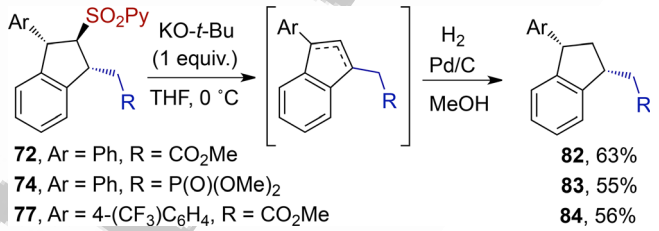
ature conditions for reductive cleavage of the sulfone group with sodium amalgam or samarium diiodide[26] failed to produce the desired desulfonylated indane derivatives. For example, the reaction of **63** and **72** with Na(Hg) established, unexpectedly, that cleavage of the 2-Py–S bond took place instead of the alkyl–S bond, leading to the corresponding indane-2-sulfinates **78** and **79**, respectively (Scheme 7). Although these sulfinates were sufficiently stable for isolation and characterization by ^{1}H NMR spectroscopy, they turned brown upon standing for several hours at room temperature and decomposed. Nevertheless, both sulfinates could be converted *in situ* into the corresponding methyl sulfone derivatives **80** and **81** in synthetically useful yields by methylation with iodomethane.

We were pleased to find, however, that a base-promoted desulfonylation proceeded smoothly in those indanes having an aromatic substituent at C-3, thereby further qualifying the synthetic utility of this pro-



Scheme 7. Desulfonylation attempts with sodium amalgam.

cedure. For example, treatment of derivatives **72**, **74** and **77** with KO-*t*-Bu (1 equiv.) in THF at 0 °C afforded in all cases a 1:1 mixture of the two regioisomeric alkenes resulting from β-elimination, for which standard catalytic hydrogenation conditions provided the corresponding *cis*-1,3-disubstituted indane derivatives **82**–**84** in moderate yields (55–63%) with excellent stereoselectivity (Scheme 8).



Scheme 8. Base-promoted desulfonylation/hydrogenation to afford *cis*-1,3-disubstituted indane derivatives.

In summary, we have developed a Pd-catalyzed method to alkenylate remote *ortho* C–H bonds of benzyl and phenethyl sulfone derivatives with electron-deficient olefins. The reaction is tolerant of substitution at the benzylic position, with no appreciable loss of enantiomeric purity when starting from chiral non-racemic phenethylamine derivatives. The process is enabled by the use of a (2-pyridyl)sulfonyl directing group that also allows for a quick and efficient assembly of indane derivatives having a variety of substitution patterns and up to three contiguous stereogenic centers with high degree of stereocontrol.

Experimental Section

Typical Procedure for the *ortho* C–H Alkenylation Reaction: Synthesis of 10

A screw-capped test tube was charged with sulfone **5** (39.2 mg, 0.15 mmol), $Pd(OAc)_2$ (3.32 mg, 0.015 mmol, 10 mol%) and 1-fluoro-2,4,6-trimethylpyridinium triflate (87 mg, 0.3 mmol, 2.0 equiv.) and phenyl vinyl sulfone (28 mg, 0.165 mmol, 1.1 equiv.). The mixture was placed under a nitrogen atmosphere (evacuated and flushed with nitrogen three times) before DCE (1.5 mL) was added. The mixture was heated to 110 °C for 16 h before it was allowed

to cool to room temperature, diluted with CH_2Cl_2 (10 mL) and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (cyclohexane-EtOAc, 5:1) to afford **10** as a pale yellow solid; yield: 47 mg (74%); mp 106–108 °C.

Compound characterization data are available in the Supporting Information.

Typical Procedure for the Cyclization Reaction: Synthesis of Indane 64

To a solution of **42** (52 mg, 0.15 mmol) in dry THF (1.5 mL), cooled to 0 °C and under a nitrogen atmosphere, was added a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 300 µL, 0.15 mmol). The resulting mixture was stirred at 0 °C for 15 min (TLC monitoring) before a saturated aqueous solution of NH_4Cl (5 mL) was added. The aqueous phase was extracted with EtOAc (3×5 mL) and the combined organic phase was washed sequentially with water (5 mL) and brine (5 mL) before it was dried ($MgSO_4$) and concentrated to dryness. The residue was purified by flash chromatography (cyclohexane-EtOAc, 1:1) to give **64** as a white solid; yield: 44 mg (85%); mp 130 °C (decomp.).

Compound characterization data are available in the Supporting Information.

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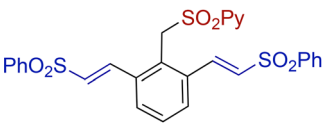
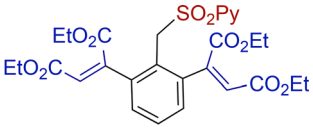


85, 86%



86, 81%

under otherwise identical conditions to those shown in Table 1 resulted in a clean diolefination reaction (products **85** and **86** in the formula below).

[25] See the Supporting Information. CCDC 1436280, CCDC 1436281, CCDC 1436282 and CCDC 1436283 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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Palladium-Catalyzed Remote *ortho*-C-H Alkenylation of Alkyl Aryl Sulfones: Access to Densely Functionalized Indane Derivatives

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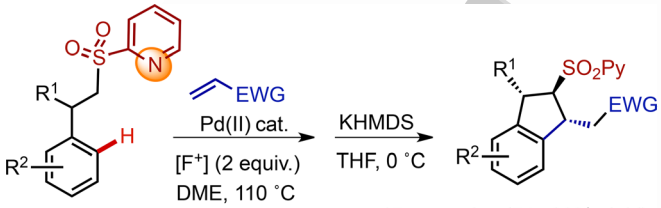

15 examples (54 – 89% yield)
>97% diastereoselectivity

([F+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate)