ACS Catalysis 9.11 (2019):10567-10574

DOI: https://doi.org/10.1021/acscatal.9b02768

Metal- and Photocatalysis to Gain Regiocontrol and Stereodivergence in Hydroarylations of Unsymmetrical Dialkyl Alkynes

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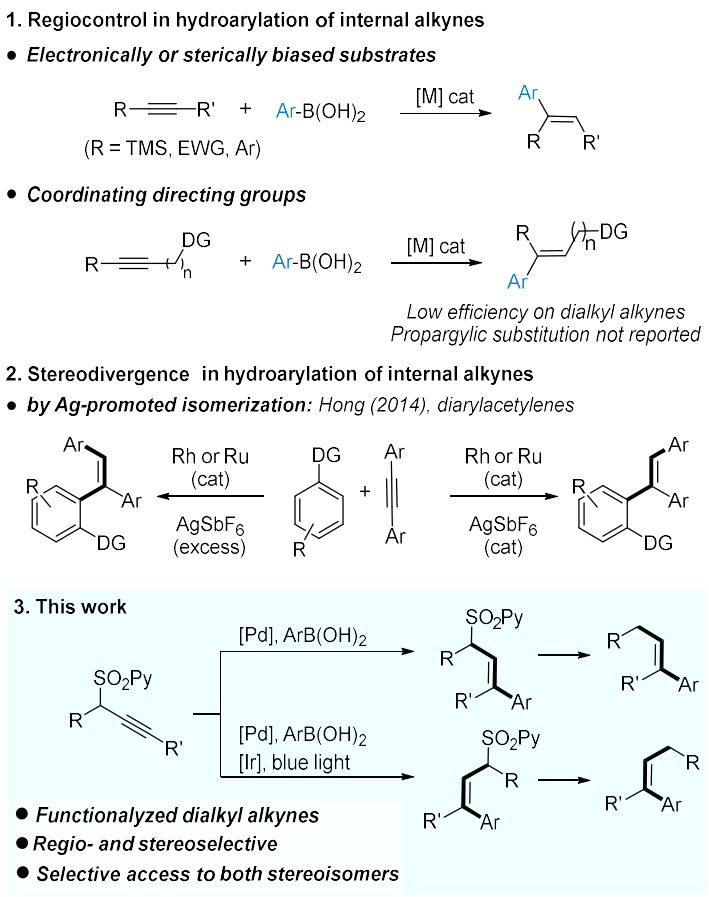
ABSTRACT. We report on a regioselective, stereodivergent catalytic hydroarylation of unsymmetrical dialkyl alkynes with arylboronic acids that allows highly selective access to either *E*- or *Z*- diastereoisomer of trisubstituted alkenes. The *E*-selectivity is achieved through *syn*-carbopalladation of the Ar-Pd species followed by protodepalladation in which a 2-pyridyl sulfonyl (SO_2Py) directing group enables complete control of the regioselectivity. Access to the complementary stereochemistry is achieved through a tandem Pd/Ir sequence, which includes hydroarylation and *E*→*Z* photoisomerization. Lastly, facile removal of the directing group by reduction, Julia-Kocienski olefination, or Cu-catalyzed C(sp^3)-C(sp^2) or C(sp^3)-C(sp^3) cross coupling, allowing for the selective preparation of stereodefined olefins and dienes.

KEYWORDS: alkyne hydroarylation, regioselectivity, stereodivergence, tandem photo/metal catalysis, removable directing group, photocatalytic alkene isomerization.

INTRODUCTION. The transition metal-catalyzed functionalization of alkynes by catalytic addition of X–Y species across triple bonds is arguably the most direct means to build multifunctional olefins.[1] Despite impressive recent momentum in this field driven by the discovery of new reactivity, control over regioselectivity when employing unactivated unsymmetrical internal alkynes continues to be one of the main challenges of this chemistry.[2] The vast majority of reported protocols rely on electronically biased alkynes, (Ar-C≡C-alkyl or EWG-C≡C-R) to attain site-selectivity.[1] In contrast, unsymmetrical dialkyl alkynes are noticeably absent from most contributions and, when present, typically provide lower yields and/or poorer selectivities. A second issue arises from the fact that stereoselectivity is generally dictated by the *syn*-addition of a catalytic R-M species across the alkyne:[3] although this topic has captured the focus of recent research efforts, the opposite stereochemistry is most often not accessible in a direct fashion.[4] Furthermore, stereodivergent methods that enable access to either stereoisomer from the same substrate are still rare yet highly sought after in organic synthesis.[5]

These two limitations can also be found in hydroarylations of internal alkynes,[6] reactions of great value for the direct preparation of trisubstituted alkenes. Firstly, catalytic hydroarylations using arylboron reagents are particularly attractive and have been intensively studied,[7] although only isolated examples that rely on the use of nonremovable directing groups provide high levels of regiocontrol on unsymmetrical dialkyl alkynes (Scheme 1.1).[8,7a,7g,7i,7j,7l,7t] Notably, Engle and co-workers recently reported on a highly regioselective Pd-catalyzed *syn*-hydroarylation of internal alkynes using a removable bidentate directing group.[9] However, unsymmetrical dialkyl alkynes were found to provide modest yields. Secondly, as for stereocontrol, the ability to synthesize Z-

alkenes –the formal of *anti*-hydroarylation products– using this approach is yet at a primitive stage,[10] and we have not been able to find reports on the application of *anti*-addition reactions to unsymmetrical dialkyl alkynes. In fact, to our best knowledge, a single example of stereodivergent hydroarylation of internal alkynes has been disclosed.[11] This particular example exploits a directed Ru/Ag-catalyzed C-H bond cleavage (Scheme 1.2) in which the stereochemical outcome of the reaction can be switched from *E* to *Z* by increasing the silver loading. However, this report describes symmetrical diaryl alkynes only, and consequently reports on unsymmetrical dialkyl alkynes remain to be disclosed.

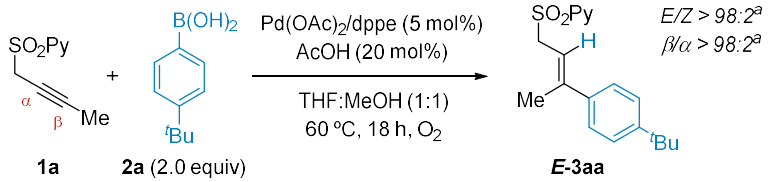


Scheme 1. Regiocontrol and Stereodivergence in Hydroarylation of Internal Alkynes.

We report herein the regioselective, stereodivergent hydroarylation of unsymmetrical dialkyl alkynes (Scheme 1.3). An (*E*)-selective Pd-catalyzed *syn*-hydroarylation with arylboronic acids is promoted and controlled by a SO_2Py group, whereas diastereodivergence is achieved by performing, in a tandem fashion,[12] the hydroarylation reaction with an Ir-catalyzed *E*→*Z* photoisomerization that leads to the corresponding formal *anti*-hydroarylation products. The rich chemical versatility of the regiocontrolling heteroarylsulfone facilitates further derivatization by methods that include stereoretentive Cu-catalyzed $C(sp^3)$-$C(sp^2)$ or $C(sp^3)$-$C(sp^3)$ cross couplings.

DISCUSSION. At the initial stage of this study we questioned if the SO_2Py group, a powerful regiocontroller in metal-catalyzed functionalization of alkynes,[13] might serve as directing group in hydroarylations. When we examined the reaction between model substrate **1a** and boronic acid **2a** (briefly summarized in Table 1, see SI for full details), we observed that the process took place in the presence of 5 mol% of $Pd(OAc)_2$/dppe as precatalyst, with 20 mol% of AcOH (which was experimentally found to promote solubility of the precatalyst), and under an O_2 atmosphere in a solvent mixture of THF:MeOH (1:1) for 18 hours (entry 1), affording (*E*)-**3aa** with complete conversion, *syn*-stereo- and β-regioselectivity. Further studies demonstrated that other solvents considerably reduced the reactivity (entry 2). Decreasing the temperature had a negative impact on the reaction (entry 3), as did the elimination of O_2 (which likely prevents catalyst deactivation into Pd^0 species, entry 4).[14] Lower catalyst loading (3 mol%, entry 5) resulted in incomplete conversion. Finally, the presence of H_2O had no significant impact on the reaction outcome (entry 6).

Table 1. β,*E*-hydroarylation: summary of optimization and control experiments

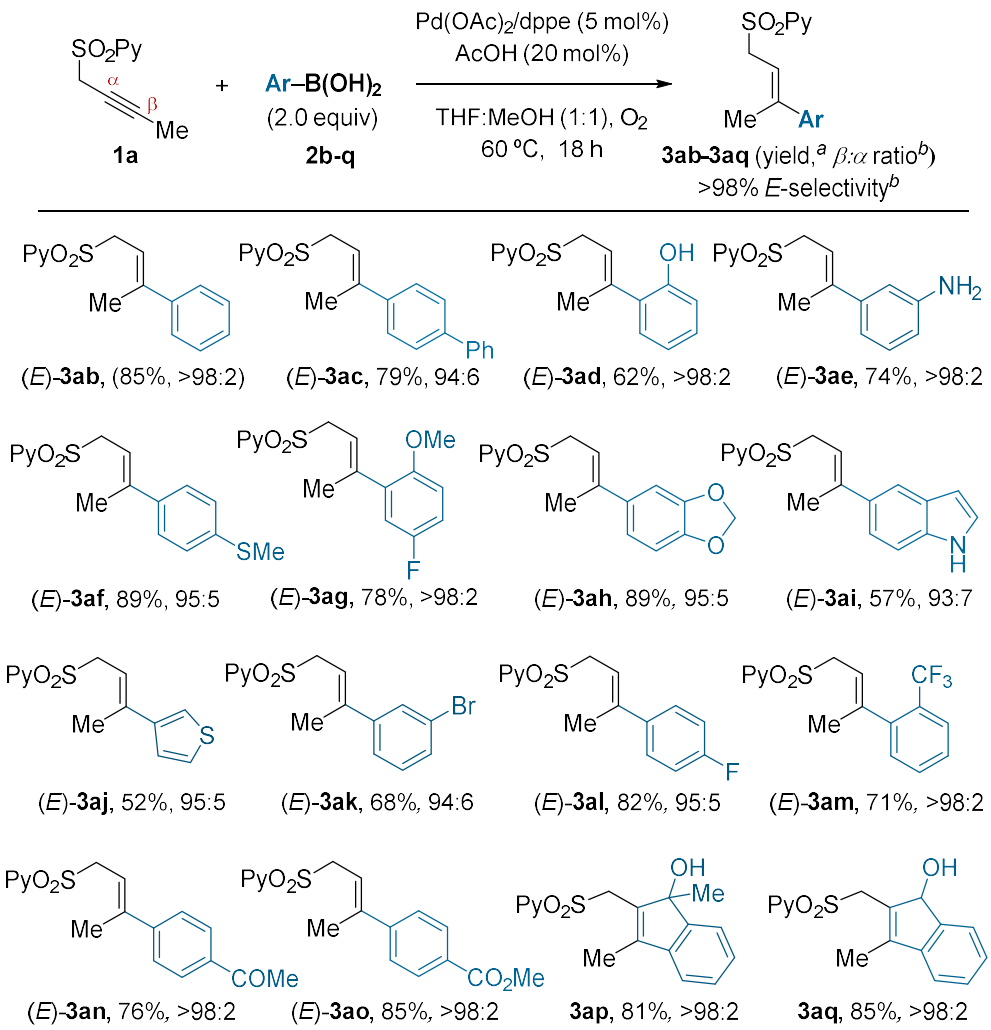


Entry	Variation	Conversion (%)[b]	Yield (%)[b]
1	-	>98	82[c]
2	CH_2Cl_2, CH_3CN, Tol	26-70	12-59
3	At 40 ºC	58	52
4	Ar atmosphere	90	76
5	3 mol % catalyst	78	65
6	THF:H_2O (10:1)	>98	80

[a]Determined in the reaction crude by ^{1}H NMR. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene (TMB) as internal standard. [c]After flash chromatography.

Substitution at the boronic acid partner was next evaluated (Scheme 2). Using the conditions shown in Table 1, plain aryl groups such as phenyl or biphenyl led to olefins (*E*)-**3ab** and (*E*)-**3ac** in high selectivity and yield. Electron-rich groups were installed satisfactorily, even allowing the presence of acidic -OH and basic -NH_2 moieties in the aryl unit ((*E*)-**3ad** and (*E*)-**3ae**). Similar results were obtained for a thioether ((*E*)-**3af**) or a methoxy substituent combined with a fluorine atom ((*E*)-**3ag**). We were pleased to find that heterocycles benzo[d][1,3]dioxole, indole, and

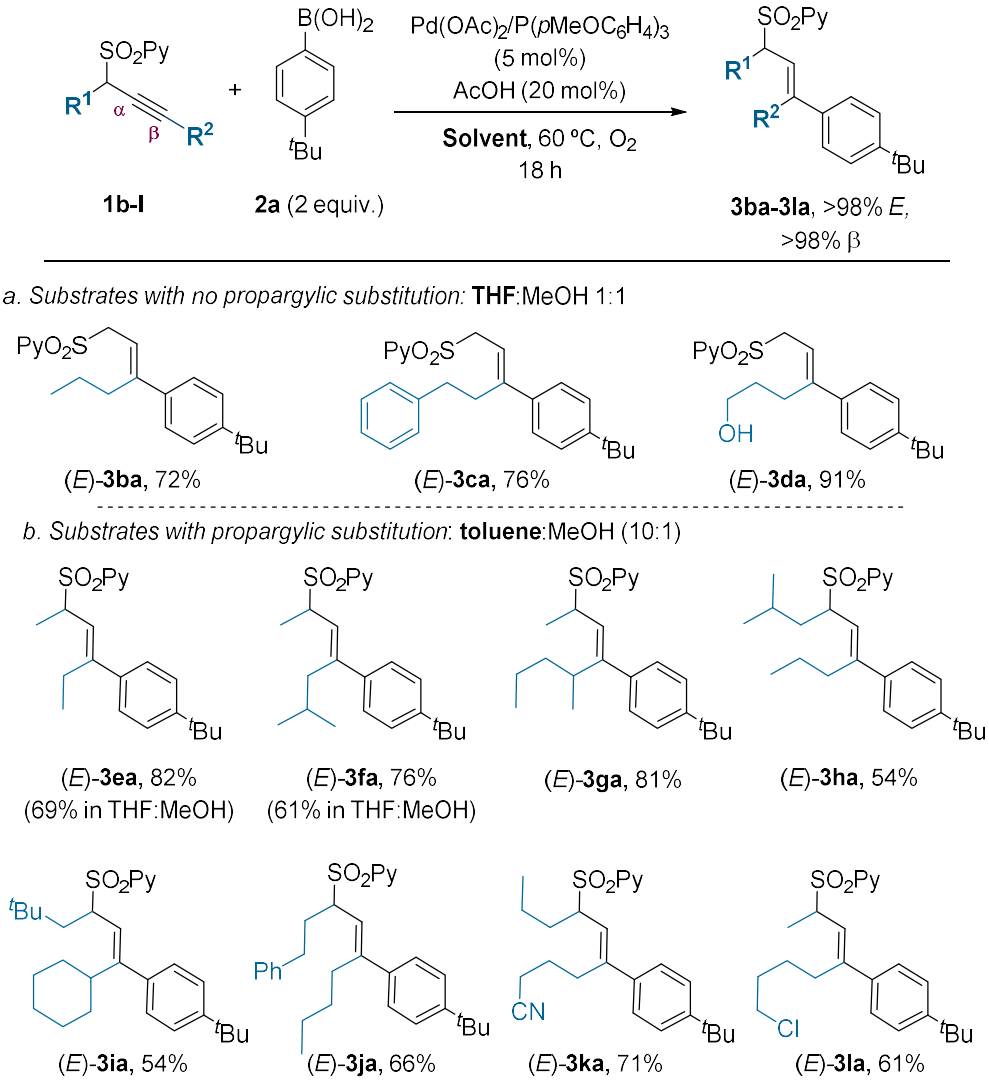
thiophene rings could also be installed, and afforded olefins (*E*)-**3ah,** (*E*)-**3ai** and (*E*)-**3aj** in good to very good yields (52-89%). Potentially sensitive groups in Pd-catalyzed transformations (and/or useful handles for further elaboration) such as an aryl bromide or aryl fluoride were found to be compatible with the reaction conditions, leading to the corresponding hydroarylated products in good yield when *m*-Br was tested (68%, (*E*)-**3ak**), and high yield in the case of the p-F derivative and (82%, (*E*)-**3al**). The introduction of other electron withdrawing groups such as CF_3, COMe, and CO_2Me resulted in very good selectivities and yields ((*E*)-**3am,** (*E*)-**3an** and (*E*)-**3ao**). Notably, decoration of the aryl ring with electrophilic substituents such as a methylketone and aldehyde at the *ortho* position resulted in formation of bicyclic sulfones (*E*)-**3ap** and (*E*)-**3aq**. These products can be explained by insertion of an aryl-Pd across the alkyne, which evolves towards the carbocyclization product via alkenyl-palladium attack to the carbonyl moiety.[15]



Scheme 2. *E*-stereoselective arylation of propargylic sulfones: boronic acids. [a]After flash chromatography. [b]Determined by ^{1}H NMR in the reaction crude.

Once we had established that a breadth of boronic acids reacts efficiently with model substrate **1a**, we investigated potential substitution patterns at the propargylic sulfone (Scheme 3). As expected from the very limited number of precedents on the hydroarylation of dialkyl alkynes, this study proved somewhat challenging when replacing the methyl substituent by longer and more complex alkyl chains.[7i,9] This was indeed the case and substrate **1b**, having an *n*Pr substituent, afforded (*E*)-**3ba** with poor regioselectivity under the standard conditions (α/β = 1:3, not shown, see Supporting

Information for details). Reoptimization of the ligand system showed that the use of electron-rich, monodentate phosphines was crucial, with P(*p*-$MeOC_6H_4)_3$ in a 1:1 Pd/L ratio leading again to complete conversion and regioselectivity (the Pd/L ratio was found to be crucial to obtain high conversion, see Supporting Information for details), affording (*E*)-**3ba** in 72% yield and >98% of regio- and *syn*-selectivity (Scheme 3a). With this ligand, substrates holding different alkyl chains reacted cleanly to afford the corresponding olefins (*E*)-**3ca-3da**. We then took on the hydroarylation of substrates bearing alkyl substituents at the propargylic position, a pattern not yet explored in the relevant literature. A first study on substrates **1e** and **1f**, bearing a methyl group next to the SO_2Py unit, afforded the corresponding olefins (*E*)-**3ea** and (*E*)-**3fa** in good yields (69 and 61 %, respectively). However, switching from THF to toluene as solvent resulted in a noticeable bump in reactivity (82 and 76 %, respectively). For that reason, we continued the study using Toluene:MeOH 10:1 as solvent mixture. The reaction was shown to tolerate different degrees of alkyl substitution, such as branching at the β-position of the alkyne ((*E*)-**3ga**). Increasing the steric bulk to *i*Bu or even neopentyl resulted in a slight drop in reactivity, although (*E*)-**3ha** and (*E*)-**3ia** were still obtained stereo- and regiochemically pure in 54 % yield in both cases. The reaction was also amenable to phenyl rings ((*E*)-**3ja)**, and even potentially problematic functional groups such as a primary alcohol ((*E*)-**3da)**, a nitrile ((*E*)-**3ka**), or even a primary alkyl chloride ((*E*)-**3la**).



Scheme 3. *E*-stereoselective arylations of substituted propargylic sulfones. Yields after flash chromatography. Ratios determined by ^{1}H NMR in the reaction crude.

We next conducted computational studies to shed light on the role of the ligands dppe and P(*p*-MeOC$_6$H$_4$)$_3$ on the regioselectivity observed in the hydroarylation process. A NBO analysis of **1b** corroborates the assumption that propargyl sulfones, whether or not coordinated to a metal, are slightly polarized (free alkyne: q_α= -0.07924, q_β= +0.04972, see Supporting Information for further details). However, this polarization alone is not strong enough to control the regioselectivity of the

process:[16] the results obtained by using bidentate dppe indicate the appearance of relatively high amounts (up to 25%) of alpha isomer. In this case, our studies show that Pd^{II} adopts a square planar geometry in which the four coordination sites are occupied by ligand (two sites), Ph, and the alkyne in **1b** (Figure 1, left). A subsequent migratory insertion step would be influenced by steric interactions between the substituents in the alkyne and those around Pd, which is in agreement with our experimental observation that the regiochemistry changes from **1a** (R=Me) to **1b** (R=*n*Pr). The scenario changes when using a monodentate ligand ($P(p\text{-}MeOC_6H_4)_3$), which allows a coordinative vacancy to interact with the substrate. As shown in Figure 1 (right), the four coordination sites around Pd are occupied by ligand, Ph, and **1b**, which acts now as a bidentate ligand through the alkyne and either N or O in the sulfone fragment. This mode of coordination allows for the Pd-Ar σ-bond and the alkyne to be close to coplanarity, a necessary requirement for the insertion to take place. This chelate also places Ph and the coordinating atom in opposite ends, which prevents it from satisfying the geometrical requirements for an α-arylation process.

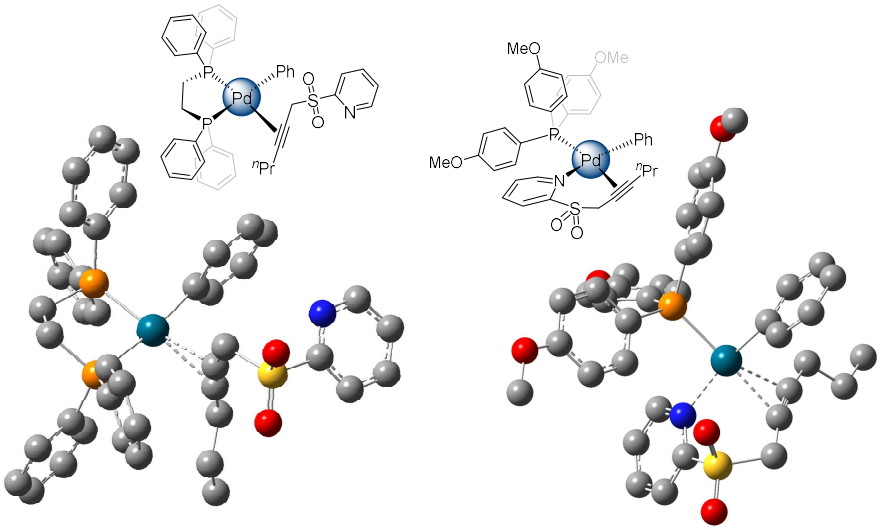


Figure 1. Coordination modes found for dppe (left) and $P(p\text{-}MeOC_6H_4)_3$ (right) with substrate **1b**.

This study points to N as the preferred coordinating atom (Figure 2): although intermediate **II** (bound by O) is 0.8 kcal/mol lower than **I** (bound by N), the TS that leads to the insertion product **III** (**TS$_{I-III}$**) is 2.5 kcal/mol more stable than **TS$_{II-IV}$**. Additionally, the insertion product **III** is 5.6 kcal/mol lower than **IV**, which indicates that chelation via N favors the insertion process both kinetically and thermodynamically. In agreement with this calculation, we observed that the hydroarylation of phenylsulfone **4**, in which only coordination through O is possible, led to incomplete conversion to (*E*)-**5** (56% after 18 hours at 60 ºC, Scheme 4). Along the same lines, a competition study between **4** (SO_2Ph) and **1b** (SO_2Py) led to exclusive hydroarylation of the latter ((*E*)-**3ba**).

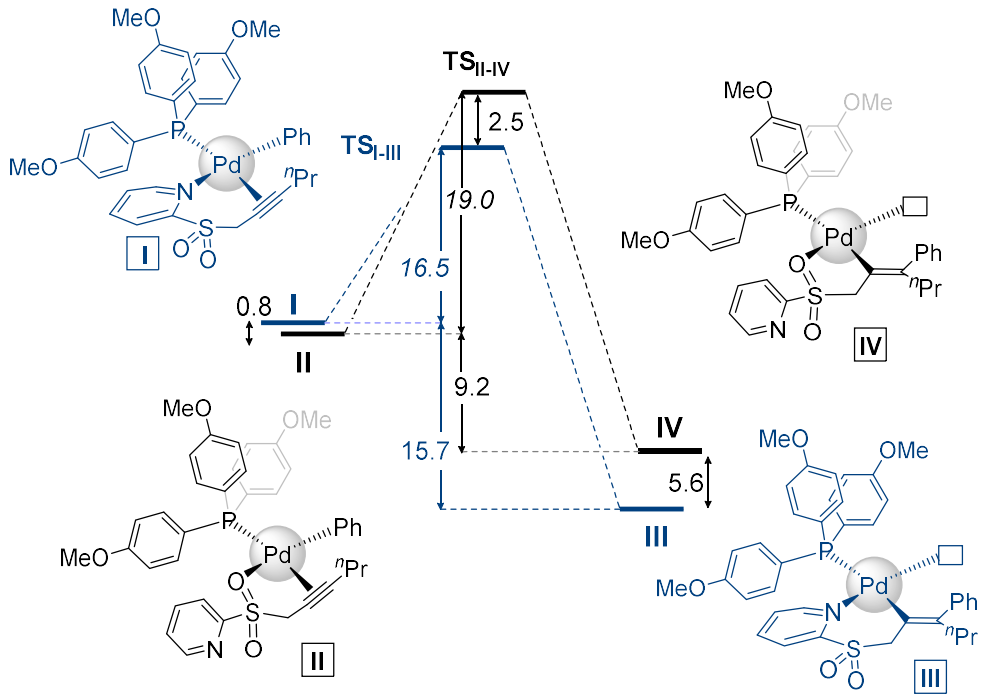
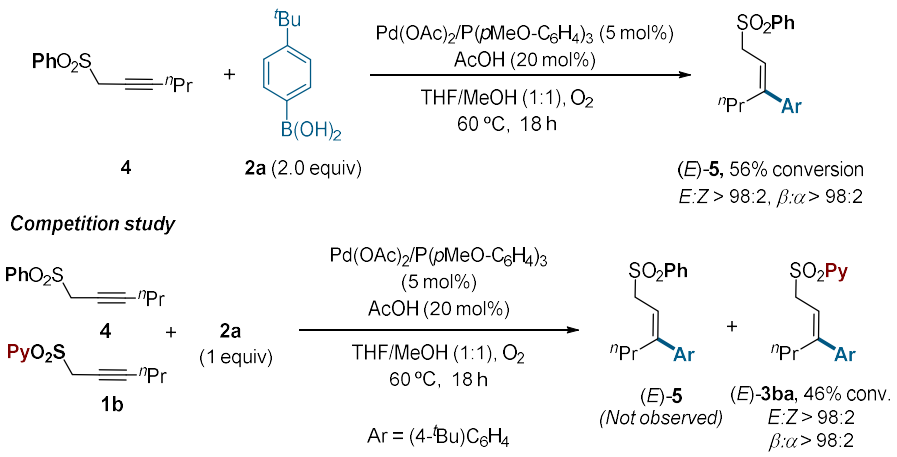


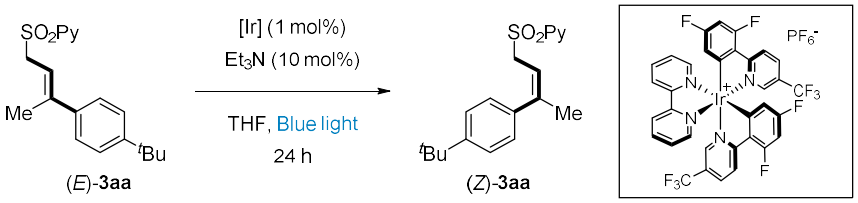
Figure 2. Energetic profile of the insertion step. ΔG (kcal mol^{-1}) are calculated at B3LYP/6-31G(d) (C,H,N,O, S,P), LANL2DZ (Pd) level in THF (PCM). Activation energies are shown in italics.



Scheme 4. Phenyl vs. 2-pyridyl propargylic sulfones.

In pursuit of a methodology that could provide access to both stereoisomers, we next considered that *access to the stereocomplementary version of the reaction would be feasible if the catalytic cycle that renders the thermodynamic product (E isomer) could be coupled to a kinetically -driven transformation.* In this regard, taking into account the styrene obtained in the process, a photocatalyzed *E-Z* photoisomerization could provide a means to solve this problem.[17] To explore this possibility, we exposed the isolated allyl sulfone (*E*)-**3aa** to light irradiation with different photocatalysts (see Supporting Information for details), and observed that using Ir{*d*FCF$_3$ppy}$_2$(bpy)]PF$_6$ (1 mol%) in THF in the presence of Et$_3$N (10 mol%) and under blue light irradiation led to (*Z*)-**3aa** with complete conversion after 24 h (Table 2, entry 1). Control experiments determined the crucial role of both the Ir photocatalyst and blue light irradiation (entries 2 and 3, respectively). Although the role of Et$_3$N in the reaction is not clear at this point, we observed that its absence led to incomplete conversions (entry 4). Remarkably, further screening of the reaction conditions showed that this *E* to *Z* isomerization could be performed in the presence of O$_2$ (entry 5).[18]

Table 2. Conditions for *E*-*Z* photoisomerization and control experiments.

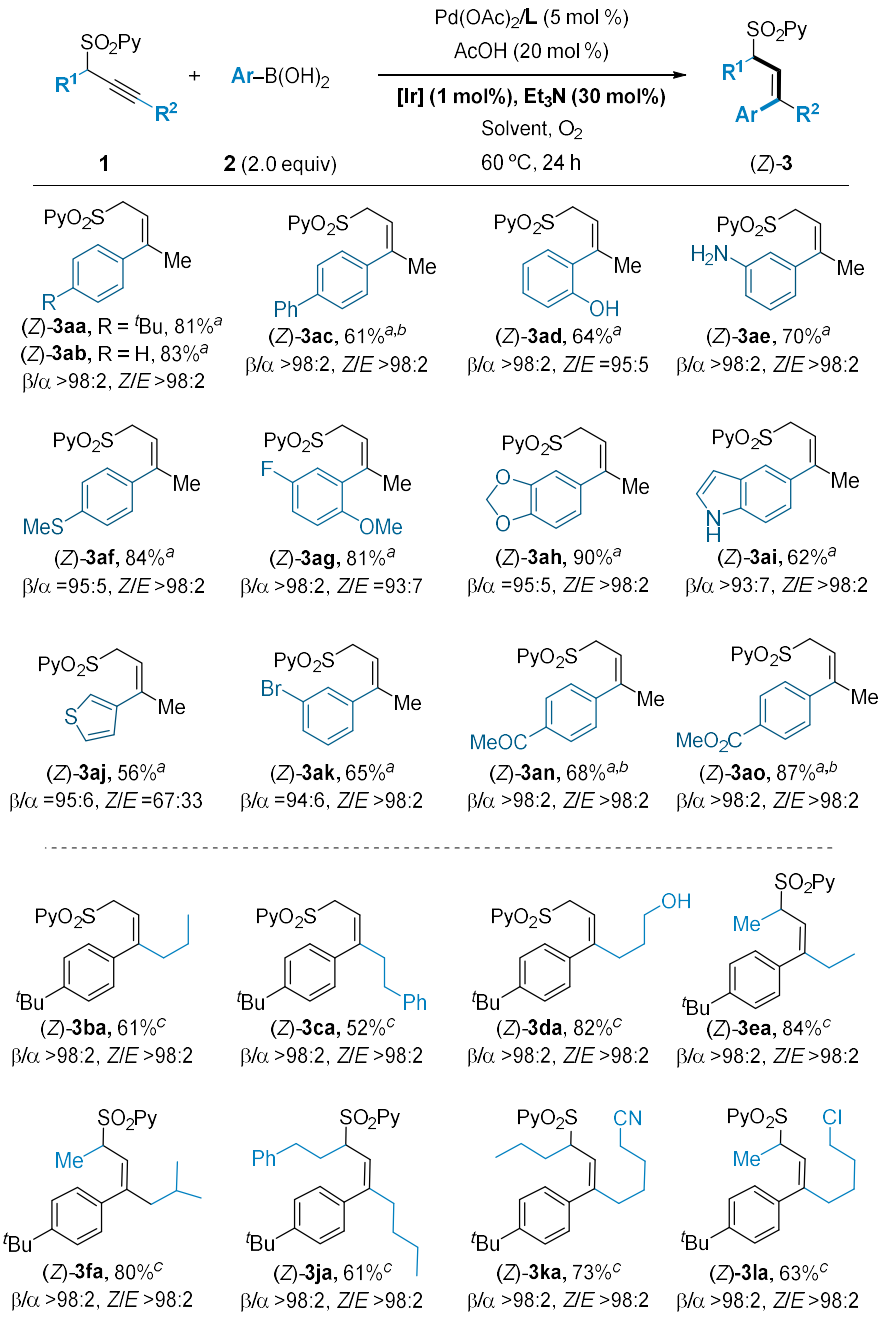


Entry	Variation	Conversion (%)[a]	Yield (%)[a]
1	-	>98	>98
2	No Ir photocatalyst	<2	<2
3	No irradiation	<2	<2
4	No Et_3N	85	81
5	O_2 instead of Ar	>98	>98

[a]Determined by ^{1}H NMR in the reaction crude using 1,3,5-trimethoxybenzene (TMB) as internal standard. Blue light = 450 nm.

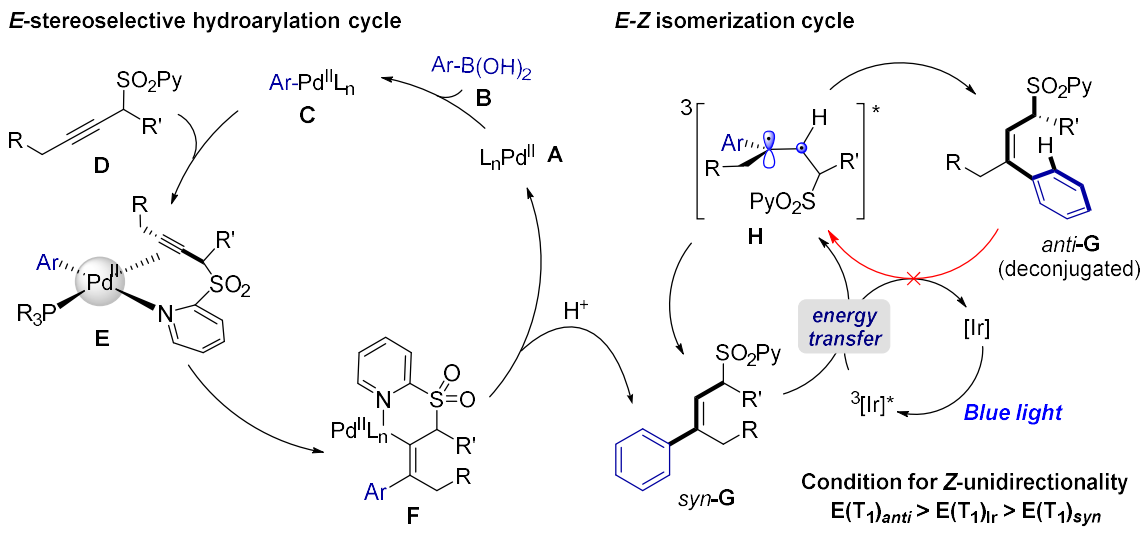
The observation that the isomerization reaction could be run in an O_2 atmosphere was particularly important, since it led us to reason that a tandem sequence that included both processes (hydroarylation and isomerization) could be feasible. We tested this hypothesis on the reaction of model substrate **1a** with boronic acid **2a** (Scheme 4): to our delight, we observed that (*Z*)-**3aa** was obtained in 81% yield, only 1 point below the yield obtained for the corresponding *E*-hydroarylation process (see Table 1). This tandem sequence, which constitutes a formal *anti*-stereoselective hydroarylation of alkynes,[19] was next tested on a number of representative alkynes

and boronic acids (scheme 5). We verified that the excellent reactivity observed in Schemes 2 and 3, was not altered under the new reaction conditions and followed the same patterns in terms of solvent and ligand: (*Z*)-alkenes were obtained in the majority of the cases studied as single stereoisomers, regardless of the substitution at the alkyne. Incomplete isomerization was detected only in two instances: (1) *ortho*-substitution ((*Z*)-**3ad** and (*Z*)-**3ag** (*Z*/*E* = 95:5 and 93:7, respectively). (2) the thiophene derivative (*Z*)-**3aj** (*Z*/*E* = 2:1).



Scheme 5. *Z*-Stereoselective hydroarylation via tandem catalysis. Isolated yields after chromatography. β/α and *E*/*Z* ratios determined by ^{1}H NMR in the reaction crude. [a] L = dppe, solvent: THF/MeOH 10:1. [b] $Ir(ppy)_3$ was used as photocatalyst. [c] L = P(*p*-$MeOC_6H_4$)$_3$, solvent: Tol/MeOH 10:1.

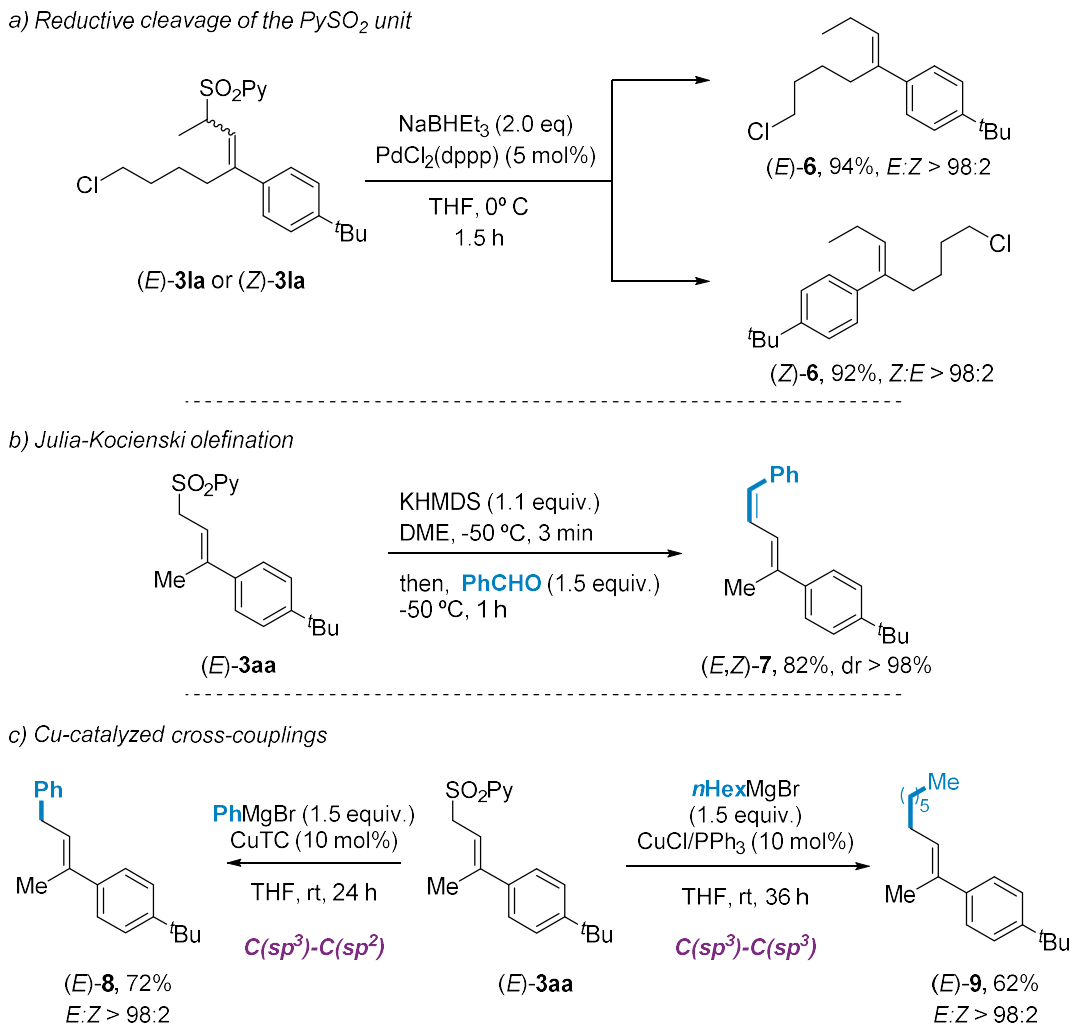
Mechanistic proposal. A tentative reaction mechanism is outlined in Scheme 6: in it, a first Pd-catalyzed *syn*-hydroarylation regiocontrolled by the SO_2Py group is followed by *E-Z* isomerization via Ir-photocatalysis. With respect to the hydroarylation mechanism, several reports in the literature propose the participation of Pd-H species as catalytically active intermediates.[15] However, as mentioned above, the use of 2-formyl-, or 2-acetylphenylboronic acids delivers the corresponding 1,2-dicarbofunctionalization product, which would presumably originate from the insertion of Ar-Pd complexes instead of Pd-H. Therefore, we propose that the hydroarylation process would start by formation of Ar-Pd intermediates **C** from the Pd(II) precatalyst **A** and the $ArB(OH)_2$ acid **B**. In the presence of a monodentate $P(p\text{-}MeOC_6H_4)_3$, subsequent coordination of substrate **D** through the alkyne and the pyridyl unit (see DFT studies above) would lead to formation of intermediate **E**, in which the alkyne and the aryl ring are disposed in a *syn* relationship. This arrangement enables the β-regioselective insertion to take place, leading to the alkenyl-Pd species **F**. Finally, protodemetallation of **F** delivers the *syn*-hydroarylated product *syn*-**G**, and regenerates the Pd(II) active species **A**. In a parallel cycle, the Ir-photocatalyst exposed to blue light irradiation is excited towards a triplet excited state ($^3Ir^*$), and made available for interaction with **G** via an energy transfer process.[17] As a result, the excited state of styrene **H** is achieved and the subsequent relaxation toward the ground state would generate either the *syn*-**G** or *anti*-**G** isomer, respectively. However, due to a steric deconjugation of the styryl fragment in *anti*-**G**, the energy transfer from $^3Ir^*$ to a styrene unit is not feasible.[17a] As a direct consequence, only the *syn*-isomer reaches the excited state. In this scenario, there is an accumulation of the *anti*-**G** isomer because the isomerization reaction is irreversible. Overall, this process constitutes a formal photo-controlled, unidirectional *anti*-hydroarylation sequence in which the selectivity is a result of a kinetic control.



Scheme 6. Plausible tandem catalytic cycle for the Pd- catalyzed *syn*-hydroarylation and subsequent Ir-catalyzed photoisomerization. $E(T_1)$ = energy of the triplet excited state.

One of the key advantages in using SO_2Py over other families of directing groups pertains to its rapid removal or transformation, which renders this auxiliary moiety "traceless". Selected examples of this rich versatility are compiled in Scheme 7. Firstly, we explored possibilities for the reductive cleavage of the heteroaryl sulfone. When we treated stereochemically pure samples of either (*E*)-**3la** or (*Z*)-**3la** with Pd^{II}(cat.)/$NaBHEt_3$ we obtained the corresponding complementary alkenes (*E*)-**6** or (*Z*)-**6** in excellent yields (>90%) and in stereochemically pure form. We next explored the behavior of our allylic sulfones under Julia-Kocienski olefination conditions, and observed that the reaction of substrate (*E*)-**3aa** under typical conditions for this transformation allowed access to a diene (*E*,*Z*)-**7** as a single diastereoisomer (Scheme 7b). Finally, we tested the ability of the SO_2Py unit to serve as leaving group in Cu-catalyzed allylic substitution reactions. In particular, we studied the possibility of performing $C(sp^3)$-$C(sp^2)$ and $C(sp^3)$-$C(sp^3)$ cross-couplings between allylsulfone (*E*)-**3aa** and PhMgBr or HexMgBr as coupling partners ((*E*)-**8** and

(*E*)-**9**, respectively, Scheme 7c). We were pleased to find that both reactions took place in good yields, again fully preserving the stereochemistry of the double bond.



Scheme 7. Removal of the directing group: Selected synthetic transformations of allylsulfones. Stereoselectivities were measured in the ^{1}H NMR reaction crude. Reaction yields are given after purification by flash column chromatography.

In conclusion, a tandem β-regioselective, stereodivergent hydroarylation process of dialkyl-substituted internal alkynes has been developed. While the SO_2Py unit serves as powerful promoter

in the hydroarylation process, the use of monocoordinated, electron-rich P(*p*MeOC$_6$H$_4$)$_3$ as ligand is crucial to create the ideal scenario for complete regiocontrol and high reactivity. Access to the stereocomplementary version of the reaction can be easily achieved through a tandem sequence that combines a Pd-catalyzed cycle to form the thermodynamic product (*syn* isomer), and a Ir-catalyzed, kinetically-driven *E-Z* photoisomerization. Both processes tolerate diverse structural motifs, including electron-rich, electron-poor, acidic, basic, or heterocyclic substituents. The auxiliary heteroaryl sulfonyl group can be removed by straightforward, highly selective methods that yield unsaturated compounds of diverse configuration.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data, and complete DFT studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTES

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Spanish *Ministerio de Economía, Industria y Competitividad* and *Fondo Europeo de Desarrollo Regional* (Project: CTQ2015-66954-P, MINECO/FEDER, UE) and *Ministerio de Ciencia, Innovación y Universidades (Agencia Estatal de Investigación)*/FEDER (Project: PGC2018-098660-B-I00) for financial support. J.C. thanks the *Ministerio de Educación, Cultura y Deporte* (MECD) for a *FPU* fellowship. M.T.Q. thanks MINECO for a *Juan de la Cierva Incorporación* fellowship. The *Centro de Computación Científica* (UAM) is acknowledged for generous allocation of computer time.

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