Interplay between the Directing Group and Multifunctional Acetate Ligand in Pd-Catalyzed \textit{anti}-Acetoxylation of Unsymmetrical Dialkyl-Substituted Alkynes

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ABSTRACT: The cooperative action of the acetate ligand, the 2-pyridyl sulfonyl (SO$_2$Py) directing group on the alkyne substrate, and the palladium catalyst has been shown to be crucial for controlling reactivity, regioselectivity, and stereoselectivity in the acetoxylation of unsymmetrical internal alkynes under mild reaction conditions. The corresponding alkenyl acetates were obtained in good yields with complete levels of \textit{β}-regioselectivity and \textit{anti}-acetoxypalladation stereocontrol. Experimental and computational analyses provide insight into the reasons behind this delicate interplay between the ligand, directing group, and the metal in the reaction mechanism. In fact, these studies unveil the multiple important roles of the acetate ligand in the coordination sphere at the Pd center: (i) it brings the acetic acid reagent into close proximity to the metal to allow the simultaneous activation of the alkyne and the acetic acid, (ii) it serves as an inner-sphere base while enhancing the nucleophilicity of the acid, and (iii) it acts as an intramolecular acid to facilitate protodemetalation and regeneration of the catalyst. Further insight into the origin of the observed regiocontrol is provided by the mapping of potential energy profiles and distortion–interaction analysis.

KEYWORDS: multifunctional ligand, ligand-assisted proton shuttle, acetoxylation of alkynes, unsymmetrical dialkyl alkynes, metal–ligand cooperativity, directing group

\section*{INTRODUCTION}

Catalytic reactions controlled by the action of ligands playing active roles besides stabilizing and tuning the metal, commonly known as multifunctional ligands, are capturing increasing attention in synthetic chemistry.\textsuperscript{1} The ability of carboxylate ancillary ligands to switch denticity, thereby facilitating reactions alongside the metal, has been widely exploited in some catalytic transformations.\textsuperscript{2} For example, acetate ligands have enabled mechanisms for C–H activation alternative to direct oxidative addition by acting as an inner-sphere base to assist deprotonation of the C–H bond concomitant with M–C bond formation, which is referred to as concerted metalation–deprotonation (CMD) or amphiphilic metal–ligand activation (AMLA).\textsuperscript{3} Another general class of related mechanism refers to proton transfer between two different ligands without involving any metal hydride known as ligand-to-ligand hydrogen transfer (LLHHT).\textsuperscript{4} However, in this type of reaction, most often the protonated ligand subsequently leaves the metal to afford the product. Alternatively, it could remain bonded to the metal and still have active participation as an intramolecular acid at other stages of the catalytic cycle, a mechanistic variation termed as a ligand-assisted proton shuttle (LAPS).\textsuperscript{5} This strategy is neither restricted to carboxylate ligands nor to C–H activation. Capitalizing on this concept, the application of metal–ligand interaction in the catalytic functionalization of alkynes would be translated into more efficient and selective transformations (Scheme 1a). Recently, Zhang and co-workers have described a gold-catalyzed \textit{anti}-carboxylation of alkynes using an amide-containing phosphine ligand, which directs the attack of the incoming carboxylic acid via hydrogen bonding.\textsuperscript{6} This ligand–reagent interaction not only makes the addition reaction pseudointramolecular in nature but also enhances the nucleophilicity of the acid (Scheme 1b). In addition, the protonated amide that remains at the coordination sphere of the metal subsequently serves as an intramolecular proton source for protodeauration, thereby accelerating the catalyst

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that Pd(OAc)₂ delivered the corresponding acetoxylated product Z-2a in 86% isolated yield, with complete β-regio- and anti-stereoselectivities after 1 h at 80 °C (entry 1). Other precious metals with a high affinity toward alkyne activation such as Pt(CH₃CN)₂Cl₂ and Au(PPh₃)Cl/AgOTf delivered the product Z-2a along with considerable amounts of the byproduct 3a (entries 2 and 3, respectively). When AgSbF₆ was used as a catalyst, complete decomposition was observed (entry 4), while other metal salts such as Zn(ClO₄)₂ did not promote any reaction (entry 5). Having identified Pd(OAc)₂ as a suitable catalyst, we explored lower loadings but the
reduced yield of Z-2a was observed when using 3 mol % catalyst (41% yield, entry 6). A slight reduction in temperature to 60 °C afforded the product Z-2a in synthetically useful 76% yield, but longer reaction times were necessary to achieve full conversion (5 h, entry 7). Other palladium(II) sources lacking any acetate ligand such as PdBr₂, Pd(acac)₂, Pd(TFA)₂, and Pd(CH₃CN)₂Cl₂ provided the product in very low yield or completely suppressed the reaction, resulting in decomposition of the starting material (entries 8–11), which points toward an important role of the acetate ligand. In addition, no product was detected if palladium was omitted in the reaction (entry 12).

Formation of ketone 3a led us to question whether it arises from enol acetate deprotection or from a competing attack of water onto the corresponding π-complex intermediate. To gain an insight into this aspect, we performed the reaction of 1a catalyzed by AuCl(PPh₃)/AgOTf but in the presence of Pd(OAc)₂, as a cocatalyst (5 mol %). Interestingly, this change led to a dramatic increase in selectivity toward the acetoxylation product 2a from 2a/3a = 62:38 to 94:6 (Table 1, entry 1). This result provides compelling evidence that ketone 3a arises from the attack of water present in AcOH onto the π-complex intermediate, followed by protodemeta lization and also suggests that the acetate ligand on Pd(OAc)₂ may play an important role in controlling chemoselectivity. Even when extra 10% v/v water was added to the reaction mixture under Pd(OAc)₂ catalysis, the acetoxylation product was formed with good selectivity (2a/3a = 86:14, entry 14). The addition of extra water (10% v/v) in the presence of a combination of gold and palladium catalysis under otherwise identical conditions revealed significant loss of selectivity, likely due to competing Au-catalyzed hydration (2a/3a = 52:48, entry 15).

Then, to test the role of the SO₂Py directing group in controlling reactivity and selectivity, substrates bearing at the propargylic position related groups with different electronic and coordinating properties were screened under the optimized conditions (Scheme 2a). The SO₂Ph analogue 1b proved to be unreactive, being fully recovered after 1 h, and an identical result was found for alkyne 1c, an electronically similar isomer of 1a carrying the 4-pyridyl sulfonyl group. These results highlight the essential role of the coordinating 2-pyridyl unit for ensuring not only regiocontrol but also reactivity. Interestingly, the lack of reactivity showed by the 2-pyridyl sulfonyl alkyne 1d emphasizes the cooperative directing role of both the sulfonyl-tethering group and the 2-pyridyl moiety, presumably by weakening its metal-coordinating ability to facilitate catalytic turnover.

The strong reliance of alkyne acetoxylation on the directing effect of the SO₂Py moiety could be exploited to achieve chemoselective functionalization of alkynes. This hypothesis was validated in an intermolecular competition reaction between 1a and 4-octyne under the standard reaction conditions, which revealed that only 1a underwent smooth acetoxylation, providing 2a in 80% yield and complete β-regioselectivity (Scheme 2b), with no acetoxylation of 4-octyne being detected. This result points toward an essential role of the SO₂Py group in promoting acetoxylation.

With suitable conditions for the acetoxylation of substrate 1a in our hands, we next questioned the need for using AcOH as a solvent by examining the effect of solvent in the reaction of 1a in the presence of 2 equiv of AcOH (Table 2). In comparison with the use of AcOH (entry 1), a dramatic decrease in reactivity was observed under nonpolar solvents such as toluene (7%, entry 2). Slightly better reactivity was observed when switching to more polar solvents such as 4-CF₃-C₆H₄ or 1,2-dichloroethane, albeit the yield was not synthetically useful (21%, entries 3 and 4). Interestingly, highly polar solvents such as dimethylformamide (DMF) or PrOH that could act as a stabilizing ligand occupying open coordination sites on the metal proved to be detrimental to reactivity, completely inhibiting the product formation (entries 5 and 6). In this case, we hypothesized that the catalytically active Pd(OAc)₂ species could interact with the solvent through hydrogen bonding, thus precluding the activation of the incoming carboxylic acid during the nucleometalation of the alkyne. The same negative result was observed when 1,4-dioxane was used as a solvent (entry 7). However, when 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was employed, the product Z-2a was obtained in 46% yield (entry 8). Using these conditions, the isolated yield of Z-2a could be further improved to 61% upon increasing the reaction time to 18 h (entry 9). These results strongly suggest that a drastic depletion of the reactivity was observed when using a solvent different from AcOH, with the exception of HFIP, thus proving the challenging nature of this transformation.

### Scheme 2. Importance of the Directing Group and Competition Experiment

**a) Role of the directing group**

![Diagram](https://example.com/diagram.png)

**b) Competition acetoxylation experiment between 1a and 4-octyne**

![Diagram](https://example.com/diagram.png)

### Table 2. Solvent Effect in the Acetoxylation of 1a

| Entry | Solvent     | Yield (%) |
|-------|-------------|-----------|
| 1     | AcOH        | 86        |
| 2     | toluene     | 7         |
| 3     | 4-CF₃-C₆H₄ | 21        |
| 4     | DCE         | 21        |
| 5     | DMF         |           |
| 6     | PrOH        |           |
| 7     | 1,4-dioxane | 46        |
| 8     | HFIP        | 61        |

* Determined by ¹H NMR spectroscopy in the reaction crude.  
* Reaction run for 18 h.
The effect of ligands in the acetoxylation of 1a was also investigated (Scheme 3). In this study, we decided to use HFIP as a solvent (conditions of entry 9 in Table 2) to favor the complexation of the metal to the added ligand and minimize possible interference caused by a large excess of AcOH. The examination of a variety of mono- (PPh₃ and PCy₃) and bidentate (dppe and dppbz) phosphines commonly used in organic synthesis and pincer-type nitrogen ligands such as bis(imino)pyridines ([⁵PDI] completely inhibited the reaction. Interestingly, X-type pyridine-based ligands such as 2-hydroxypyridines/2-pyridones delivered the product Z-2a but only in low yield (L₈−L₁₀, 23–28%). This type of ligand is able to assist the dissociation of trimeric palladium acetate [Pd₃(OAc)₆].²³ In contrast, pyridine-2-carboxylic acid derivatives were totally ineffective ligands (L₁₀−L₁₀). We speculate that the external ligand might hinder the simultaneous coordination of palladium to the substrate (in a bidentate fashion) and the acetate ligand, which could be key to enabling catalysis. Consequently, the ligandless conditions found initially in Table 1 (entry 1) were selected as optimal for the acetoxylation reaction.

**Structural Scope for the anti-Acetoxylation.** Having established an efficient catalytic system for the β-acetoxylation of substrate 1a, we set out to investigate the versatility of the reaction toward more challenging substrates (Scheme 4). Gratifyingly, this method is compatible with the presence of an alkyl substituent at the propargylic position without erosion of the reaction yield (83%, Z-4). The use of substrates with larger alkyl substituents was also well-tolerated, maintaining the exceptional levels of regio- and stereoselectivities (products Z-5 and Z-6, 74 and 72% yield, respectively). Larger alkyl groups at the propargylic position, such as 'Bu, phenethyl, or even 'Bu, were also amenable to the reaction without affecting the regio- or stereoselectivity (Z-7-9, S3–73%). Importantly, potentially sensitive functional groups such as alkyl halide or nitrile were also accommodated with no observable impact in yield or selectivity (products Z-10–12, 61–79% yield). Interestingly, the SO₂Py directing group is capable to override the inherent electronic bias due to conjugation imposed by the aromatic substituent in internal aryl-substituted alkynes, since this class of alkynes typically undergoes insertion with opposite regioselectivity.⁹ As illustrated for products Z-13–16, the excellent β-regioselectivity was maintained for some representative aryl alkynes regardless of the electronic character of the aromatic ring. In all cases studied, the corresponding acetoxylation products were isolated as single regioisomers in synthetically useful yields, even for substrates containing strong electron-withdrawing groups (Z-15 and Z-16, 52 and 50%, respectively). Unfortunately, terminal alkynes were incompatible, largely producing catalyst deactivation. On the other hand, primary hydroxyl- and carboxylic acid-containing alkynes proved not to be suitable in this reaction, resulting in deactivation of the catalyst or decomposition of the starting material (not shown, see the Supporting Information, SI for further details).

**Kinetic Analysis.** To further understand the role of acetic acid in the reaction, we performed a kinetic analysis to determine the presence of a primary kinetic isotope effect (KIE) by monitoring the acetoxylation of substrate 1a in AcOH and AcOD-d₄ by independent experiments (Figure 1). From this study, we observed a clear effect in the reaction rate for the acetoxylation of propargyl sulfone 1a, in which a slower formation of the acetylated product took place when acetic acid-d₄ was employed both as a solvent and reagent (Figure 1a,b). In addition, the plot of the ln(100-conversion) vs time for the nondeuterated and deuterated kinetic profiles led to a linear fit, resulting in a pseudo-first-order kinetics from which a

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**Scheme 3. Ligand Effect in the Acetoxylation Reaction**

| Ligand | Reaction Conditions | Product | Yield |
|--------|---------------------|---------|-------|
| No ligand | HFIP, 80 °C, 18 h | Z-2a | 61% |
| PPh₃ (10 mol%) | AcOH (2.0 equiv) | Z-2a | 23% yield |
| PCy₃ (10 mol%) | HFIP | Z-2a | no reaction |
| dppe (L₅, 5 mol%) | AcOH | Z-2a | no reaction |
| dppbz (L₄, 5 mol%) | HFIP | Z-2a | no reaction |

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**Scheme 4. Representative Substrate Scope for the Acetoxylation of Unsymmetrical Internal Alkynes Employing the SO₂Py Group as a Regiocontroller**

![Scheme 4](https://doi.org/10.1021/acscatal.2c00710)
primary KIE of 5.5 was obtained (Figure 1c, see the SI for details). These results suggest that either the addition of the acid or the protodepalladation step could be the rate-determining step of the reaction.

**Computational Analysis.** To gain insight into the reaction mechanism, we conducted a computational analysis considering several pathways. These calculations were carried out using the M06-L functional. For gas-phase geometry optimizations and frequency calculations, the def2-SVP basis set with effective core potential (ECP) was used for Pd, and the cc-pVDZ basis set was used for all other atoms (C, H, N, O, S). Single-point energy calculations with an SMD continuum solvation model were performed using the def2-TZVP basis set with ECP for Pd, and the cc-pVTZ basis set for all other atoms (see the SI for further details). To analyze the intrinsic reactivity of the propargyl sulfone 1a either free in solution or bound to Pd(OAc)$_2$, we first calculated the condensed Fukui functions$^{24}$ at the C$_\alpha$ and C$_\beta$ positions (Figure 2). These results showed that, albeit the triple bond is naturally polarized, it becomes more electrophilic upon Pd coordination (see the SI); in both cases, the C$_\beta$ position is more electrophilic. However, the rather low difference between the two positions (+0.028 for C$_\alpha$ and +0.051 for C$_\beta$) suggests that the selectivity toward the $\beta$-adduct cannot be exclusively accounted for by electrophilicity. Thus, we have calculated the complete reaction profiles for the $\alpha$- and $\beta$-acetoxylation (Figure 2). We found that the reaction follows a stepwise mechanism in both cases. Initially, we observed that the complexation of propargyl sulfone 1a with Pd(OAc)$_2$ is thermodynamically feasible to form the corresponding chelate species I$_2$. From this intermediate, we further explored the addition of AcOH to both positions of the C−C triple bond. The first step corresponds to the AcOH addition to the triple bond and the concomitant proton migration from the incoming AcOH molecule to one of the acetate ligands bound to Pd. From both alkenyl-palladium(II) intermediates (I$_5$ and I$_6$), intramolecular protodepalladation can take place to form the final alkenes (I$_9$ and I$_{10}$) and regenerate Pd(OAc)$_2$ upon de-coordination from the product. The selectivity is determined at the first step, given that the formation of the 6-membered palladacycle ($\beta$-addition) is kinetically $\Delta\Delta G^\ddagger = (T S-\beta-I_3)-(T S-\alpha-I_4) = -7.7$ kcal/mol) and thermodynamically (exergonic, $\Delta\Delta G_{\text{exac}} = (I_6-I_3)-(I_5-I_4) = -9.9$ kcal/mol) more favorable. In contrast, the proto-
the depalladation step proceeds very similarly for both pathways ($\Delta \Delta G^\neq = (\text{TS-H} - I6) - (\text{TS-H} - I5) = +1.7$ kcal/mol) since one AcOH is coordinated to the palladium center after the addition of the carboxylic acid. Alternative reaction pathways (coordination of an additional AcOH molecule and intramolecular syn insertion of the alkyne into the Pd–OAc bond) are discussed in the SI, none of them were found to be more favorable than the $\beta$-acetoxylation presented here. These conclusions help to understand the key role of the acetate ligand since it assists in the formation of the C–O bond during the acetoxypalladation event through proton migration. This reactivity closely resembles the more typical concerted metalation–deprotonation (CMD) pathway observed in some C–H activation processes. Therefore, the acetate ligand behaves as a multifunctional ligand during the addition of the carboxylic acid and further protodemetalation. This observation is in accordance with the lack of reactivity

Figure 2. Reaction profiles for the intermolecular $\alpha$- (magenta) and $\beta$-acetoxylation (blue). Gibbs free energies in kcal/mol at 353.15 K are given relative to the sum of all reagents (1a + AcOH + Pd(OAc)$_2$) at an infinite distance.

Figure 3. (Top) Activation energies and Gibbs free energies and distortion–interaction energy contributions at the TSs. Energies in kcal/mol. (Bottom) Distortion/interaction diagrams for the intermolecular $\alpha$- (left) and $\beta$-acetoxylation (right) projected onto the C–O distance. Vertical dashed lines mark the position of TS-\alpha or TS-\beta. [Pd] accounts for the 1a-Pd(OAc)$_2$ complex. A zoom of the region comprised between a C–O distance value of 2 and 3 Å is provided in the inset. Distances are given in Å, energies in kcal/mol.
observed when different strong coordinating ligands are present since they are not expected to be active in the proton migration event. In contrast, when 2-hydroxypyridines were employed, the reaction delivered the acetoxylated product in low yields, pointing out to the potential role as acid activators of these N-coordinating species during the proton migration.\(^\text{25}\) Additionally, this activation mode is observed in the transition state of the rate-determining step (the acetoxy palladation), thus explaining the KIE obtained when compared with the reaction kinetics in AcOH and AcOD-d\(_4\).

To further understand the origin of the differences in the activation energies of the first step of the reaction, we analyzed the energy profiles by means of the distortion/interaction model.\(^\text{26}\) In short, this model proposes that the reaction energy at any point of the reaction coordinate can be divided into two components, one associated with the reagents’ geometry deformations (the distortion energy, \(\Delta E_d\)), and the stabilization produced when the distorted reagents interact (the interaction energy, \(\Delta E_i\)). Figure 3 shows the distortion/interaction diagrams for the \(\alpha\)- (left) and \(\beta\)-acetoxylation (right). To carry out this analysis, we divided the reaction complex into two subunits, the incoming AcOH molecule and the 1a-Pd(OAc)\(_2\) complex. While the \(\Delta E_d\) (Pd) curves (the distortion energy associated with the 1a-Pd(OAc)\(_2\) complex) are similar, the main difference between both reaction pathways lies in \(\Delta E_i\) (AcOH), which starts to increase earlier in the \(\alpha\)-addition than in the \(\beta\)-addition. In fact, at the position of TS-\(\alpha\) (recall Figure 3), \(\Delta E_d\) (AcOH) is not only larger than \(\Delta E_i\) (Pd) but also slightly larger (in absolute values) than \(\Delta E_d\), making it the predominant term for the activation energy. In contrast, for TS-\(\beta\), the contribution of \(\Delta E_d\) (AcOH) is minimal. This critical difference can be related to the moment at which proton migration takes place. For the \(\alpha\)-addition, the lower electrophilicity of the C\(_\gamma\) position requires that O–H dissociation occurs in an early stage to increase AcOH nucleophilicity and to facilitate C\(_\gamma\)-O bond formation, but the cost of the O–H bond cleavage is larger than the gain in reactivity. In contrast, as the C\(_\beta\) position is more reactive, O–H dissociation can develop after C\(_\beta\)-O bond formation and would occur after the TS-\(\beta\), so the energy required to O–H dissociation is clearly compensated by \(\Delta E_i\) along the whole pathway.

The above-mentioned factor determines that the proton migration plays a critical role in favoring the \(\beta\)-acetoxylation over the \(\alpha\), as for the \(\alpha\)-addition the O–H cleavage is required in an early stage and thus increases \(\Delta E_d\) (AcOH) to a point that it cannot be compensated by \(\Delta E_i\), while for the \(\beta\)-addition, it occurs at the end of the reaction. This can be proved easily by plotting the O–H distance against the C–O (Figure 4); in the \(\alpha\)-addition (red pathway), the O–H dissociation occurs before C–O formation and starts before the TS, while the opposite behavior is observed for the \(\beta\)-addition.

To further corroborate our hypothesis on the differential asynchronicity in the bond formation at TS-\(\alpha\) and TS-\(\beta\), we have resorted to a NBO analysis to evaluate/quantify the interaction between the two approximating moieties (Figure 5, top and bottom, respectively). For both transition states, the C\(_\gamma\)–C\(_\beta\) is no longer a triple bond, given that the C–Pd bond is already formed, and a virtual p orbital can be located over the other carbon center. However, the formation of the new C–O bond is in a more advanced state in TS-\(\beta\), as reflected by the greater second-order interaction energy between the oxygen lone pair and the carbon p orbital of the 1a-Pd(OAc)\(_2\) complex acid is broken, while the new one (with the acetate ligand) is yet to be formed. As was discussed before, the proton transfer takes place earlier in the \(\alpha\)-addition than in the \(\beta\)-addition. Consequently, the second-order interaction energy between the empty 1s orbital of the transferred proton and the oxygen lone pair of the acetate ligand is greater in TS-\(\alpha\) (276 kcal/mol) than that in TS-\(\beta\) (49 kcal/mol). On the other hand, the second-order interaction energy between the 1s\(_{\text{H}}\) and the oxygen lone pair of acetic acid is greater in TS-\(\beta\) (354 kcal/mol) than that in TS-\(\alpha\) (129 kcal/mol).

| orbital pair | TS-\(\alpha\) | TS-\(\beta\) |
|-------------|-------------|-------------|
| n\(_{\text{O1}}\) → p\(_c\) | 68 | 107 |
| n\(_{\text{O2}}\) → 1s\(_{\text{H1}}\) | 129 | 354 |
| n\(_{\text{O3}}\) → 1s\(_{\text{H1}}\) | 276 | 49 |
CONCLUSIONS

In summary, this study of the acetoxylation reaction of unsymmetrical dialkyl alkynes with AcOH shows that the cooperative effects of the palladium metal, the SO₂Py directing group at the propargylic position, and the acetate ligand play essential roles in reaction efficiency and selectivity control. The corresponding alkyl acetates are obtained with good yields and excellent level of regioselectivity (acetate delivered distal to the directing group) and anti-addition stereoselectivity. Experimental and computational mechanistic analyses suggest that the acetate ligand plays multiple important roles. It brings the AcOH near the metal–substrate complex through hydrogen bonding, enhances its nucleophilicity, and directs the attack to the alkyne in a regioselective fashion. Additionally, once protonated, it also facilitates protodematallation acting as a proton shuttle to protonate the alkylen-Pd intermediate intramolecularly. These studies revealed that the anti-acetoxy palladation of the alkyne is both a rate-determining and regioselectivity-determining step of the catalytic cycle. The two regiochemical outcomes have been analyzed in detail using the distortion/interaction model, showing that the proton migration plays a critical role in favoring the β-acetoxylation over the α-attack. These observations provide a blueprint for the rational design of more efficient methods to attain regiocontrol in the functionalization of internal alkynes through the addition of polar X—H bonds. Further studies regarding the synthetic potential of the resulting alkyl acetates and directing group transformations are under study in our laboratories and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c00710.

Experimental procedures; 1H and 13C NMR spectra for all new compounds; and DFT calculations (PDF)

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Notes
The authors declare no competing financial interest.

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\[
\begin{align*}
\text{SO}_2\text{Py} & \quad \text{Pd(OAc)}_2 \quad \text{PrOH} \quad \text{AcCH}_3 \\
\text{Me} & \quad \text{AcOH} \quad 80^\circ\text{C} \quad 35 \text{min} \\
1a & \quad \text{equil iPPrOH} \quad \text{conversion (1a / 2a)} \\
10 & \quad 23/77 \quad 29/71 \quad 58/42
\end{align*}
\]

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