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Letter

Friedel–Crafts-Type Arylation Strategy for the Conversion of Alkyl 2-((Diphenoxyphosphoryl)oxy)-2-arylacetates to α,α-Diaryl Esters

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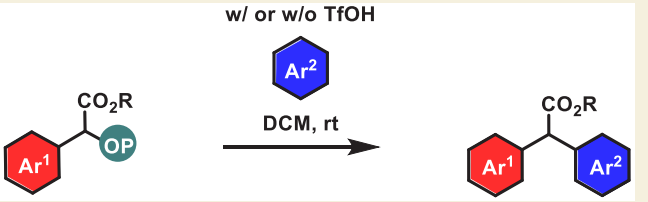
ABSTRACT: An arylation strategy allowing the conversion of alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates to α,α-diaryl esters is reported. This transformation can be promoted by TfOH when the starting organic phosphates do not carry *para*-alkoxy groups on their aryl rings, but it does not require any additives when such groups are present. These alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates can be readily accessed from the insertion of diphenyl phosphate into aryldiazoacetates.



KEYWORDS: *Phosphates, Substitution reactions, Friedel–Crafts, Arylation, O–H Insertion*

Phosphates are relatively uncommon leaving groups employed in transformations performed in a synthetic organic chemistry laboratory when compared to halides or sulfonates, which are well-established text-book benchmarks. This is a counterintuitive observation, as chemists are often inspired by nature;[1] and phosphates are arguably found involved in numerous biological processes.[2] A plausible explanation for this difference between human-based work versus naturally selected processes can derive from the chemical tools available and constraints imposed by reaction media. Organic chemists typically do not use enzyme-catalyzed reactions; and consequently, generally require the employment of reasonably reactive alkyl halides or sulfonates for their transformations performed in organic solvents. On the other hand, biochemical conditions generally use highly reactive and specific enzyme catalysts for reactions performed in aqueous media, which can compensate for the involvement of more stable phosphate compounds. Furthermore, alkyl halides or sulfonates are generally not tolerated in aqueous media because they tend to hydrolyze more rapidly. They are also more toxic, possibly leading to the alkylation and destruction of essential metabolites and enzymes.[2]

Concerning the somehow limited number of chemical transformations describing the use of phosphates as leaving groups in organic synthesis, representative reactions have been reported based on the use of catalytic or stoichiometric promoters. For instance, arylation strategies of allyl phosphates have been reported employing Cu[3] and Ni[4] catalysts (Scheme 1a); while benzyl phosphates have been arylated using Pd-catalyzed[5,6] strategies (Schemes 1b and c). Propargyl phosphates could be also arylated via Cu-based catalysis to produce either propargyl-[7] or allenyl-arenes[8] (Scheme 1d). On the other hand, representative substitution strategies involving different benzyl phosphates and arenes have been promoted using catalytic amounts of $Fe(OTf)_3$[9] (Scheme 1e), TfOH[10] (Scheme 1f), and $BF_3.OEt_2$ or $ZnCl_2$[11] (Scheme 1g).[12]

In this context, we became interested in evaluating the arylation of alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates as a potentially valuable new C–C bond-forming method while at the same time also reinforcing the ability of phosphates to be employed as competent leaving groups in substitution reactions. Furthermore, the selectivity of this method is also an interesting aspect to be considered in regard to other previous strategies[13,14] (Scheme 2a). For the synthesis of phosphates **1**, the following key elements of design were considered: (i) quaternary carbons directly attached to the oxygen atoms of the phosphate **1** seemed advantageous to prevent potential undesired substitutions at these positions (Scheme 2b); and (ii) starting substrates **1** could be potentially readily prepared from the O–H insertion of phosphates **5** into aryldiazoacetates **4**.[15] Based on this preliminary analysis, diphenyl phosphate **5a** seemed to be a particularly attractive reacting partner (Scheme 2c).

Having these considerations in mind, we started evaluating the synthesis of different alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1**, which could be readily prepared upon mixing different aryldiazoacetates **4** with diphenyl phosphate **5a** in DCM, at room temperature (Scheme 3), without requiring the use of any catalyst (see the Supporting Information for more details).

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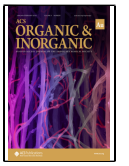
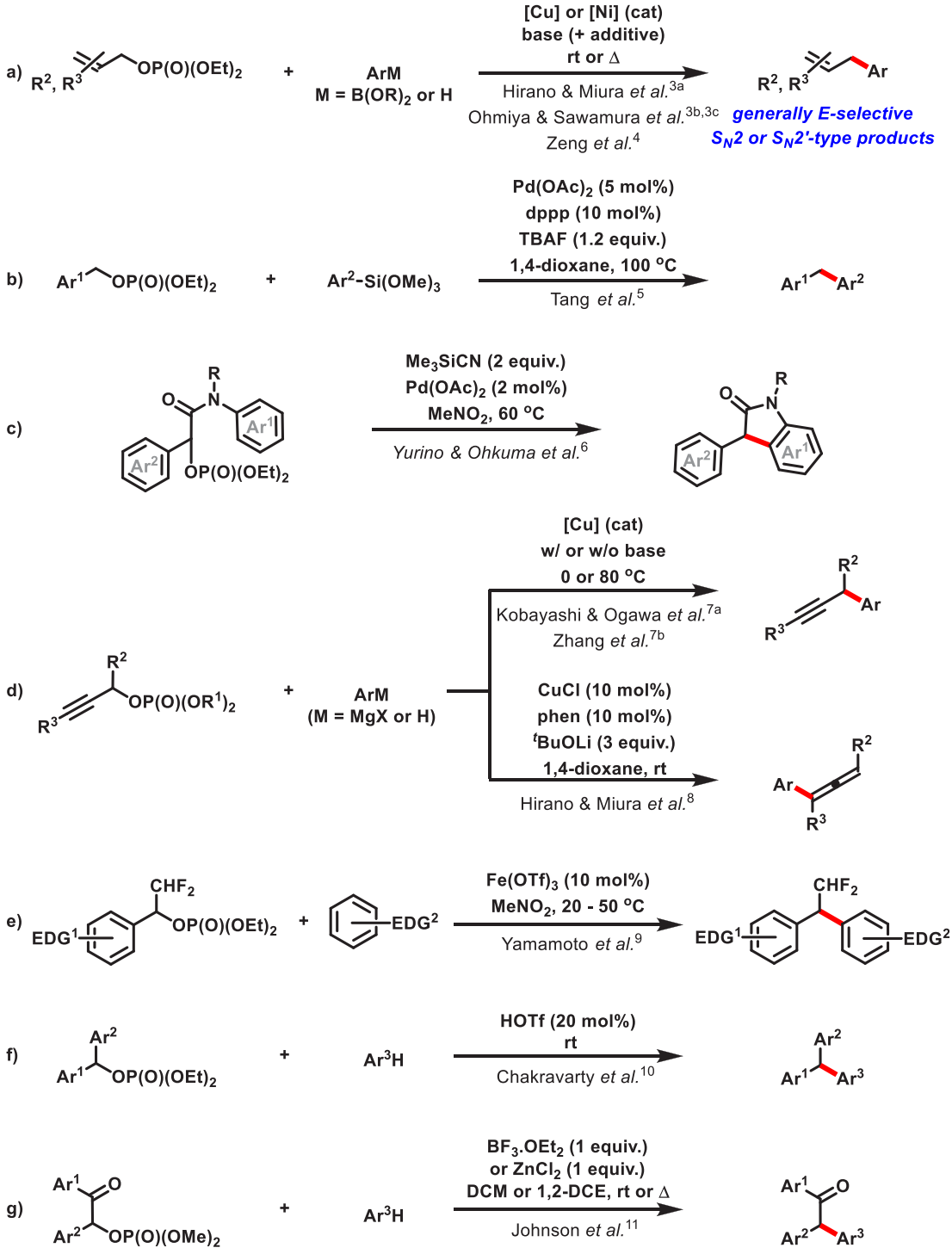


Scheme 1. Representative Arylation Methods Using Different Organic Phosphates as Reacting Partners



Overall, different alkyl groups were tolerated in the ester moiety of the diazo compound **4**, thus allowing the preparation of molecules **1a**−**1f** in good yields, 72−88%. In a similar manner, different aryl rings carrying electron-donor and acceptor functional groups were also allowed in the preparation of phosphates **1g**−**1p**, which could be accessed in a range of 50−89% yields (Scheme 3). Furthermore, additional attempts employing different diazo compounds as reacting partners, 2-diazo-1,2-diphenylethan-1-one **4q**, ethyl diazoacetate **4r**, and (diazomethylene)dibenzene **4s** produced a 74% yield for **1q**, 82% yield for **1r**, and a complex mixture for **1s**, respectively (Figure 1).

Having a general strategy to access alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1** in hand, we moved forward with our synthetic plan toward the exploration of their direct substitution using nucleophilic partners **2** under Brønsted acid activation; and TfOH was effective in promoting this reactivity (Scheme 4), while other weaker Brønsted acids AcOH, TFA and *p*-TSA.H_2O could not promote this reaction (see the Supporting Information for details). In this context, 1,3,5-trimethoxybenzene **2a** could be used as a competent

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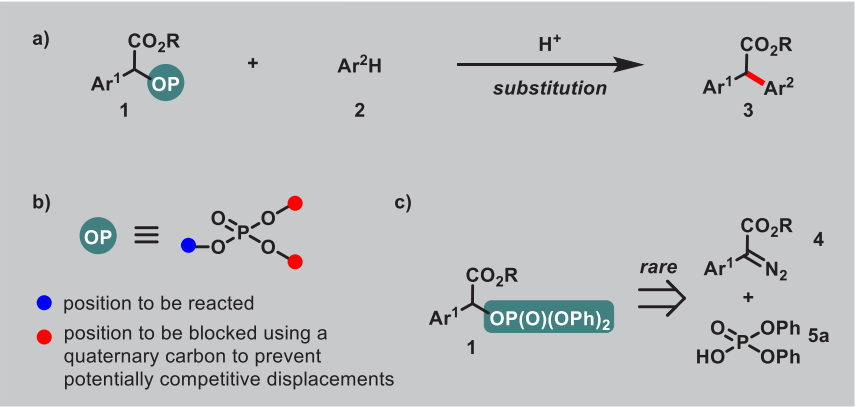
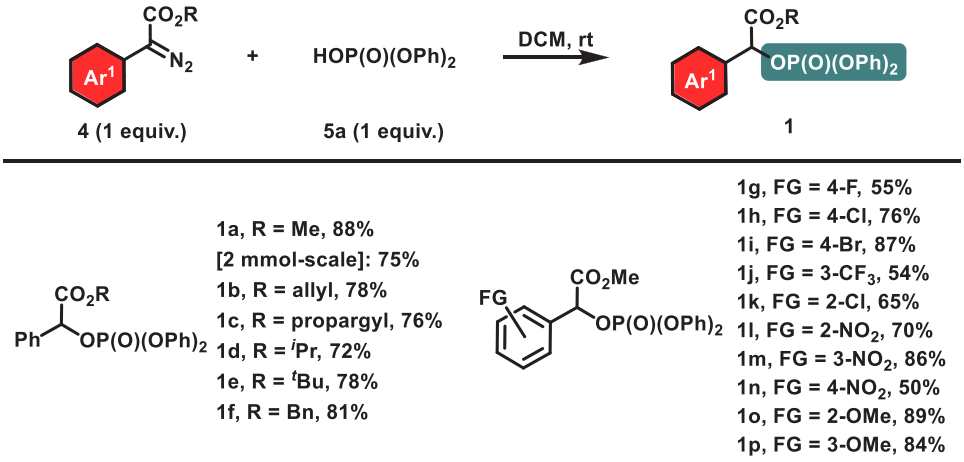
Scheme 2[a]



[a](a) Our proposed method to make new C−C bonds via the arylation of alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1** with non-prefunctionalized arenes **2** aiming at the synthesis of α,α-diaryl esters **3**. (b) Element of design guiding the targeted reactivity of the phosphate moiety. (c) Retrosynthetic analysis for the desired starting materials, alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1**.

Scheme 3. Synthesis of Starting Phosphates 1 via O−H Insertion of Diphenyl Phosphate 5a (0.2 mmol) onto Aryldiazoacetates 4 (0.2 mmol) in DCM (0.1 M, 2 mL)



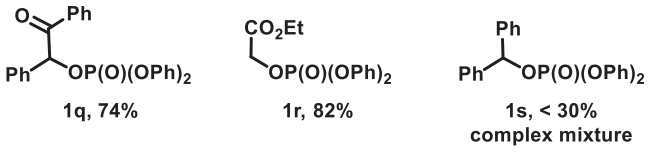


Figure 1. Evaluation of other diazo compounds for the O−H insertion of diphenyl phosphate **5a**.

nucleophile leading to the formation of the corresponding α,α-diaryl esters **3a**−**3g** in synthetically useful yields, 36−63%. The efficiency of the reaction using benzyl ester **3b** was markedly lower, 36% yield, possibly due to the lability of the benzyl ester group under strongly acidic conditions (pK_a TfOH ≈ −14).[16] In agreement with this observation, attempts to arylate phosphates having an allyl ester group (**1b**) and a propargyl ester group (**1c**) with 1,3,5-trimethoxybenzene **2a** under the same reaction conditions led to inseparable mixtures containing minor amounts of the corresponding desired compounds with their unreacted starting phosphates, along with degradation. Furthermore, phosphates carrying a 2-Cl group on the aryl ring (**1k**) and a 3-OMe group on the aryl ring (**1p**) produced only sluggish reactions affording low conversions for the corresponding desired arylated compounds **3f** and **3h**, which, after 24h of reaction, could not be separated from the corresponding unreacted starting phosphates. In addition, alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates containing a 2- or 4-NO_2 group on the aryl ring (**1l** and **1n**, respectively) also did not allow the desired transformations, as evidenced by our frustrated attempts of synthesizing **3i** and **3j**.

On the other hand, the arylation of phosphate **1q** leading to ketone **3k** could be achieved in 60% yield, while the arylation of **1r** aiming at the preparation of ester **3l** was unsuccessful. The reaction of phosphate **1a** with benzene **2b** and mesytilene **2c** produced the corresponding arylated compounds **3m** and **3n** in 97% and 75% yields, respectively. Furthermore, the use of anisole **2d** produced the corresponding arylated compounds **3o** and **3o'** as an inseparable 1:1 mixture, in a combined 82% yield. A similar outcome was also observed for the use of toluene **2e** and naphthalene **2f** as nucleophiles, thus leading to **3p** and **3p'** as an inseparable 3:1 mixture of *para*-:*ortho*-isomers in a combined 70% yield; and a 2.2:1 inseparable mixture of 1-:2-naphthyl substituted compounds **3q**:**3q'**, in a combined 87% yield. Finally, attempts to use *N*-methylpyrrole **2g** as a nucleophile aiming at the preparation of ester **3r** were unsuccessful (Scheme 4).

During our investigations aiming to convert methyl 2-diazo-2-(4-methoxyphenyl)acetate **4t** to the corresponding phos-

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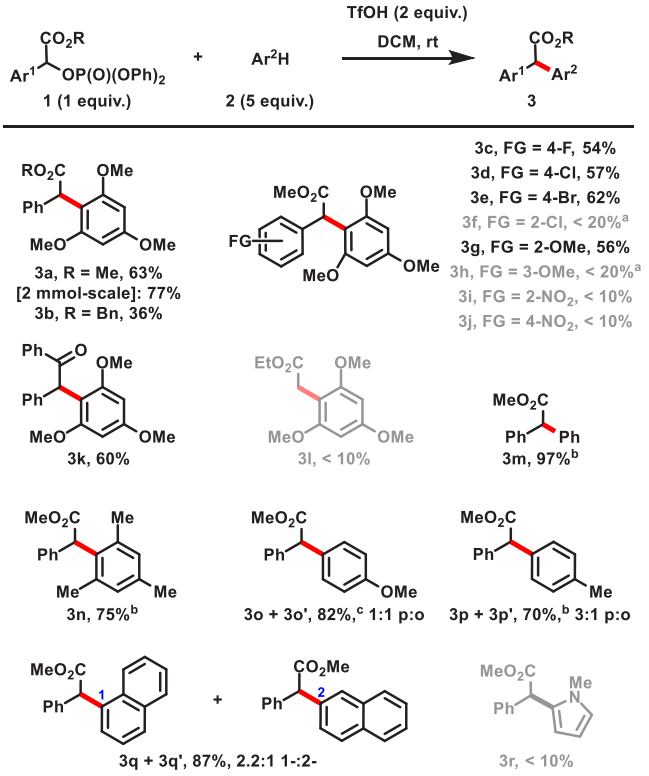
Scheme 4. Nucleophilic Substitutions of Different Arenes 2 (0.5 mmol) onto Alkyl 2-((Diphenoxyphosphoryl)oxy)-2-arylacetates 1 (0.1 mmol) Promoted by TfOH (0.2 mmol) in DCM (0.1 M, 1 mL)[a]



[a]Target compound **3** could not be isolated from unreacted starting material **1**. [b]Arene **2** employed as co-solvent with DCM. [c]Anisole was employed in 6 equiv.

phate **1t**, this target compound could be observed in the crude reaction mixture by ^{1}H NMR, but it was shown to be unstable during our attempts of isolation by flash column chromatography. Consequently, we envisioned to directly perform a reaction sequence by converting the aryl diazoesters **4t−4v** carrying electron-donor groups with diphenyl phosphate **5a** to afford the corresponding intermediates **1t - 1v**, followed by their reactions with different arenes **2** to gain access to the corresponding *α*,*α*-diaryl esters **3**. In this case, no activation of intermediate phosphate **1** with TfOH was required (Scheme 5).

In this context, we examined the use of 1,3,5-trimethoxybenzene **2a**, anisole **2d**, *N*-methylpyrrole **2g**, phenol **2h**, Boc-protected aniline **2i**, diphenylamine **2j**, aniline **2k**, and carbazole **2l** as nucleophilic arenes and diazo compounds **4t−4v** could be converted to *α*,*α*-diaryl esters **3s−3bb** as major or only compounds, in a range of 37−66% yields. Exceptions in chemoselectivity were noted when diphenylamine **2j** and aniline **2k** were employed, which led to the major or sole products obtained **3y'** and **3z**, respectively, being derived from the nucleophilic attack of their heteroatoms, rather than their aryl rings (Scheme 5).

In terms of mechanism, the O−H insertion of phosphate **5a** into aryldiazoacetates **4** likely involves the protonation of the diazo compound, followed by a substitution event promoted by the phosphate ion,[17] which is in close proximity to the classical mechanism of esterification of carboxylic acids with diazomethane.[18] For the second substitution event involving the replacement of the phosphate leaving group by a nucleophilic arene, we became interested in investigating the role of TfOH as a promoting agent. In order to study the mechanism of this reaction in more detail, we submitted an enantioenriched phosphate **1a**, 77.6:22.4 er[19] to our optimal reaction conditions in the presence of 1,3-dimethoxybenzene **2m**; and we observed a fair amount of racemization (as it could be somehow expected) for the preparation of *α*,*α*-diaryl acetate **3cc**, which was obtained in 70% yield and 62.0:38.0 er. However, it was a remarkable observation that **3cc** was produced with partial inversion of stereochemistry in regard to the starting phosphate **1a**[20] (Scheme 6). Furthermore, in the context of this mechanistic inquiry, an additional remarkable observation is that the same substitution protocol using phosphate **1r** does not afford the corresponding arylated ester **3l** (cf. Scheme 4).

Considering the highly acidic reaction conditions and the previously mentioned experimental observations, our current working hypothesis for the operating mechanism of this transformation is that the TfOH protonates the phosphate group of **1**, thus making it a better leaving group for a S_N1-like substitution reaction involving the attack of the arene nucleophile **2**. This event seems to proceed to some extension with inversion of the stereochemistry of the starting phosphate **1**, which is a feature reminiscent of a S_N2-type reaction, but this can be possibly understood here via the involvement of an intimate ion pair intermediate. In this regard, the mechanism of this substitution event can be possibly more accurately described as $D_N{*}A_N$.[21]

In the case of phosphate intermediates **1t−1v** derived from diazo compounds **4t−4v**, having at least one *para*-substituted alkoxy group in their aryl rings, it seems that this S_N1-type reaction (i.e., a Friedel−Crafts-type arylation) occurs more readily, as the presence of the electron-donor group could contribute to an increased stabilization of a putative cationic intermediate. This could be the reason the reaction proceeded in the absence of any Brønsted acids. Of note, this observation is also in agreement with a previous report from Burtoloso and co-workers.[13d] In this specific context, we have also preliminarily evaluated the realization of a catalytic protocol employing aryldiazoacetate **4t** (1 equiv) and phenol **2h** (3 equiv) employing diphenyl phosphate **5a** in 2, 10 and 20 mol % in 24 h of reaction, thus aiming at the preparation of *α*,*α*-diaryl ester **3s**. This target compound could be observed by ^{1}H NMR as the major product in the crude reaction mixture in 32%, 50% and 54% yields (using 1,3,5-trimethoxybenzene as internal reference), respectively.

In summary, we developed a Friedel−Crafts-type arylation approach to react alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1** with nonprefunctionalized arenes **2** to afford *α*,*α*-diaryl esters **3**. In the absence of electron-rich aryl rings embedded in the structure of **1**, the substitution reaction could be promoted by TfOH. Remarkably, this reaction appears to proceed via a S_N1-type mechanism displaying an intriguing partial inversion of stereochemistry of the starting phosphate **1**. However, when an *para*-substituted alkoxy group is present in the aryl ring of **1**, the arylation occurs in the absence of any additional promoter. The key substrates alkyl 2-((diphenoxyphosphoryl)oxy)-2-arylacetates **1** could be readily accessed from the O-H insertion of diphenyl phosphate **5a** into aryldiazoacetates **4**.

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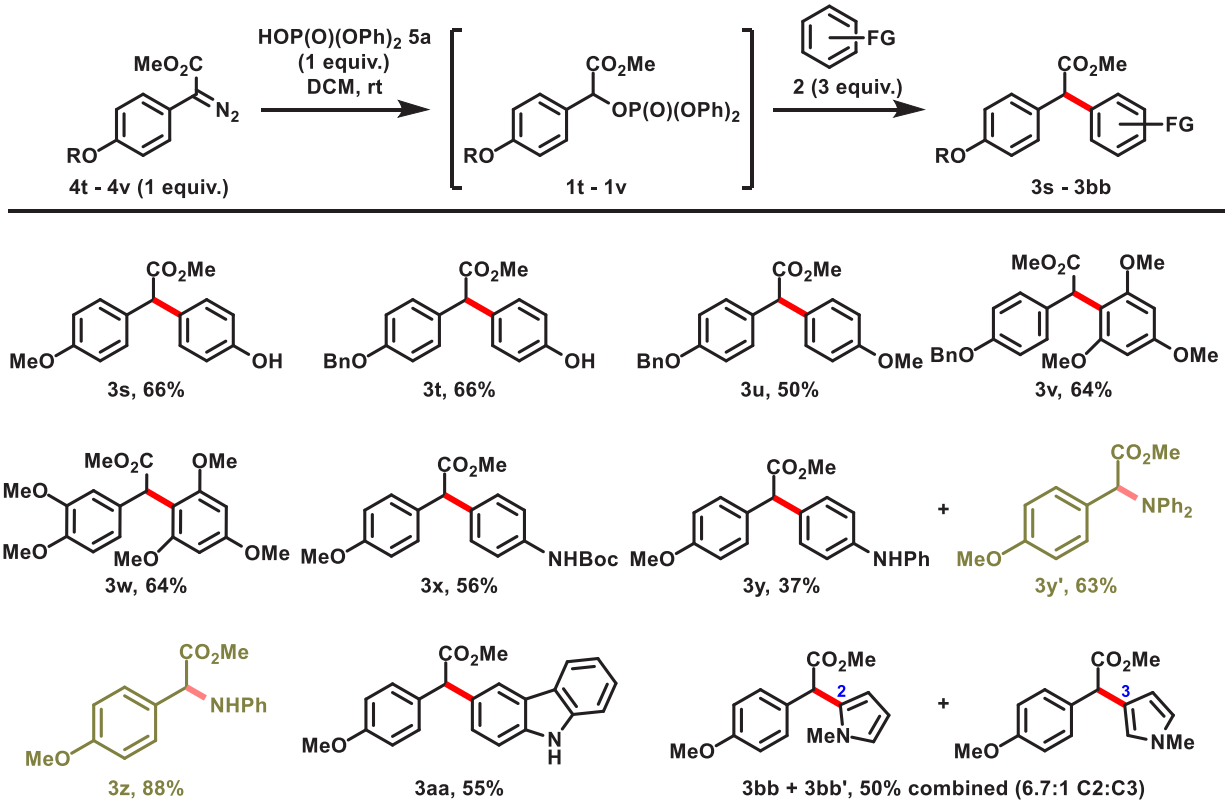
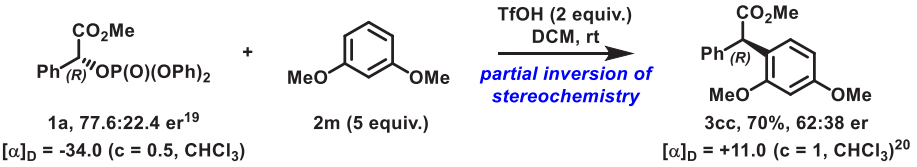
Scheme 5. Scope Accessed via a Reaction Sequence Involving Aryldiazoacetates Carrying Electron-Donor Groups 4t−4v (0.1 mmol) in the Presence of Diphenyl Phosphate 5a (0.1 mmol), Followed by the Addition of an Arene 2 (0.3 mmol) to Afford the Corresponding α,α-Diaryl Esters 3s−3bb + 3bb'



Scheme 6. Mechanistic Investigation Showing Partial Inversion of the Stereochemistry of the Initial Enantioenriched Phosphate 1a for the Arylation Event Leading to Enantioenriched α,α-Diaryl Ester 3cc



■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.3c00042.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra of all compounds\ (PDF)

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†K.C.C. and T.A.C.G. contributed equally. CRediT: **Kauê C. Capellaro** conceptualization, data curation, formal analysis, investigation, methodology; **Tales A. C. Goulart** conceptualization, data curation, formal analysis, investigation, methodology, writing-review & editing; **Rafael D. C. Gallo** conceptualization, data curation, formal analysis, investigation, methodology, writing-review & editing; **Juliana de S. Schenfel** data curation, formal analysis, investigation, methodology; **Igor Dias Jurberg** conceptualization, data curation, formal analysis,

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funding acquisition, project administration, resources, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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