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1 *anti*-Hydroarylation of Activated Internal Alkynes: Merging Pd and 2 Energy Transfer Catalysis

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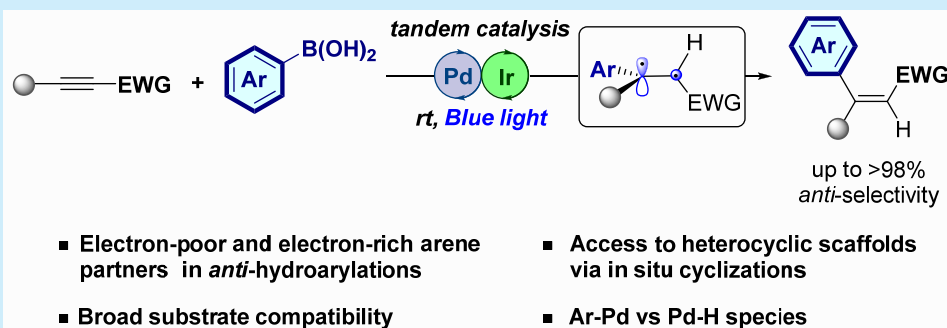
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4 **ABSTRACT:** A general catalytic *anti*-hydroarylation of electron-deficient internal alkynes compatible with both electron-poor and
5 electron-rich aryl reagents is reported. This selectivity is achieved through a sequential *syn*-carbopalladation of the alkyne by an Ar–
6 Pd species, followed by a tandem, Ir-photocatalyzed, counter-thermodynamic *E* → *Z* isomerization. The use of *ortho*-substituted
7 boronic acids enables direct access to pharmaceutically relevant heterocyclic cores via a cascade process. Mechanistic insight into the
8 involvement of Ar–Pd versus Pd–H as an active species is provided.

9 **S**tereochemically defined functionalized alkenes are essential
10 building blocks for the rapid assembly of complex molecules
11 due to their rich and versatile chemistry.¹ The catalytic direct
12 hydroarylation of electron-deficient internal alkynes such as
13 ynoates or ynones is a highly efficient means to access
14 functionalized trisubstituted arylalkenes.² Although the inherent
15 electron bias of this class of alkynes typically ensures efficient
16 regioselectivity control, an important current limitation is the
17 inability to consistently access both *syn*- and *anti*-stereoisomers
18 on demand. In this regard, there are two general strategies for
19 intermolecular hydroarylation, each of them resulting in
20 opposite stereoselectivity depending on the mechanism
21 involved. The first one, and by far the most explored, is the
22 catalytic generation of *syn*-alkenyl metal species via 1,2-insertion
23 of the alkyne into a metal–aryl bond that upon protodemeta-
24 lation yields *syn*-trisubstituted arylalkenes.^{3–6} Access to *anti*-
25 trisubstituted arylalkenes is much more challenging, with only a
26 handful of examples reported thus far (Scheme 1). Rare
27 examples of formal *anti*-carbometalation of internal alkynes
28 relying on a *syn*- to *anti*-isomerization of the initially formed *syn*-
29 carbometalation intermediate have been reported (Scheme
30 1a).⁷ However, this approach is limited in terms of the alkyne
31 scope due to the requirement of a thermodynamic driving force
32 for isomerization (e.g., a metal coordinating heteroatom to form
33 a more stable, chelated alkenyl–metal species). Furthermore, as
34 far as we are aware, no example of this type of isomerization has
35 been disclosed for electron-deficient internal alkynes.^{8,9} For this

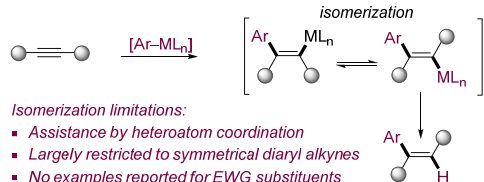
substrate class, a strategy has been reported via a Friedel–Crafts-
type mechanism that delivers *anti*-carbometalation products
(Scheme 1b), generated by formation of a π -complex between
the metal catalyst and the alkyne and subsequent outer-sphere
nucleophilic addition of an arene (in *anti*-fashion).¹⁰

Visible light photocatalysis has been utilized to promote
thermodynamically unfavorable *E* → *Z* isomerizations of alkenes
through generation of a transient, high-energy excited state.¹¹
We have recently demonstrated that merging Pd-catalyzed Ar–
B(OH)₂ hydroarylation of unsymmetrical dialkyl alkynes
bearing a 2-pyridyl sulfonyl and photocatalytic olefin isomer-
ization into a single process provides stereodivergent access to
trisubstituted alkenes.¹² It is known that the combination of
photocatalysis and metal catalysis involves interactions between
both catalytic cycles that might result in the modification of
oxidation states and geometries of intermediate species.^{13,14}
Consequently, the compatibility of two well-known metal and
photocatalytic cycles is not guaranteed. Herein, we report the
application of this tandem strategy to circumvent the problem of
hydroarylation of electron-deficient internal alkynes with

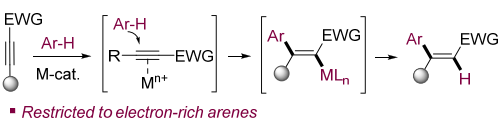
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Scheme 1. Approaches to *anti*-Stereoselective Control in Intermolecular Hydroarylation of Internal Alkynes

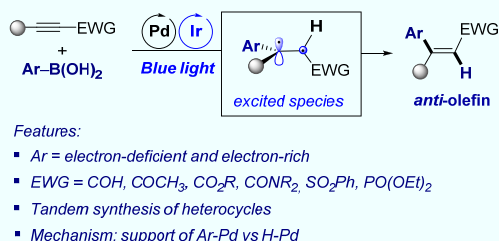
a. *anti*-Hydroarylation via syn-1,2-insertion/thermodynamic isomerization



b. *anti*-Hydroarylation via π -alkyne electrophilic activation



c. This work: *anti*-hydroarylation via tandem Pd/photocatalysis



electron-poor arenes (Scheme 1c). Control of the isomerization of 1,1-diaryllkene-containing substrates, which is a limitation of this approach, has been achieved by an in situ intramolecular cyclization that enables access to pharmaceutically relevant heterocyclic cores. Additionally, we present mechanistic experiments directed at elucidating the involvement of Ar-Pd, as opposed to Pd-H species, in the catalytic cycle. We initially studied a *syn*-hydroarylation of an alkynoate followed by photoisomerization of the resulting double bond (Table 1). The reaction between **1a** and boronic acid **2a**, in the presence of Pd(OAc)₂/dppe (5 mol %), AcOH (20 mol %), and Ir(ppy)₃ (1 mol %) as photosensitizer, in THF under blue light irradiation (465 nm) was completed after 24 h (entry 1), yielding (Z)-**3aa** as a single diastereomer (92%). Other acid such as CF₃COOH proved to be equally effective as an additive (89%)

Table 1. Tandem Pd/Ir-Catalyzed *anti*-Hydroarylation: Initial Observations

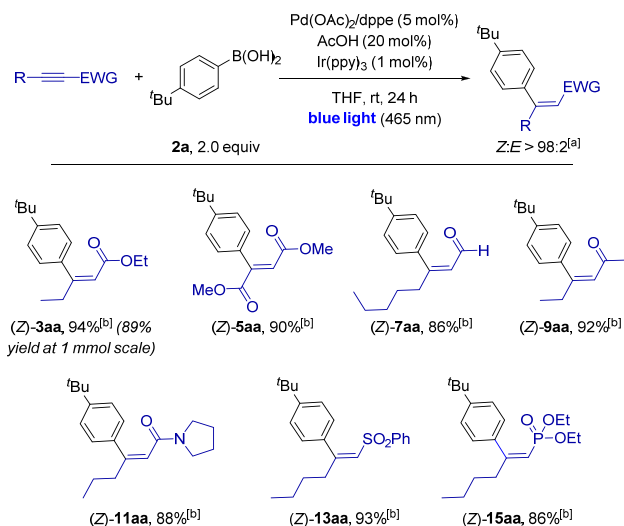
entry	variation	conversion ^a	Z/E ^a	yield ^b (%)
1	none	>98:2	>98:2	92 (89) ^c
2	no light	>98:2	<2:98	94
3	no [Ir]	>98:2	<2:98	93
4	no [Pd]	<2		
5	3 mol % of [Pd]	78	>98:2	nd
6	1 mol % of [Pd]	37	>98:2	nd
7	12 h	>98:2	58:42	nd

^aDetermined in the reaction crude by ¹H NMR. ^bAfter flash chromatography. ^cAcOH was replaced with CF₃COOH.

yield, entry 1). As opposed to most related Pd-catalyzed hydroarylations, we found that the hydroarylation step could be performed at room temperature.¹⁵ Control experiments showed the crucial role of blue light and Ir(ppy)₃ in the *E*-*Z* isomerization process (entries 2 and 3, respectively). The reaction in the absence of Pd did not take place (entry 4).¹⁶ Decreasing the Pd catalyst loading resulted in lower conversions, although photoisomerization still took place quantitatively (entries 5 and 6). Finally, shortening the reaction time to 12 h afforded complete conversion to a 58:42 mixture of olefins.

Once we demonstrated the feasibility of our hypothesis, we tested the conditions above on substrates decorated with electron-withdrawing groups (EWGs) of diverse nature (Scheme 2). Alkynes bearing groups based on carbonyl

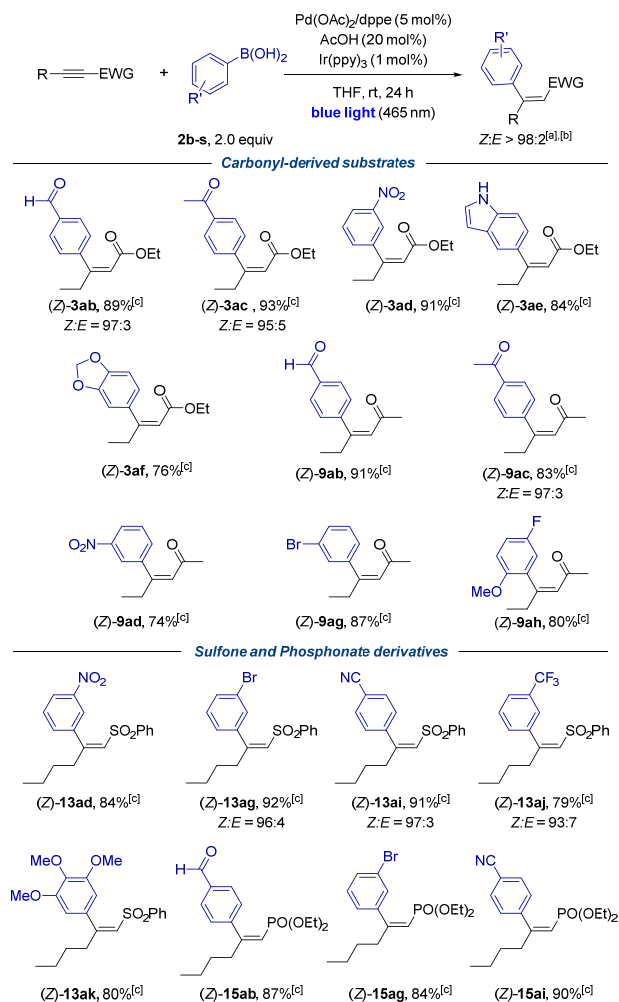
Scheme 2. EWG Substitution at the Alkyne Partner



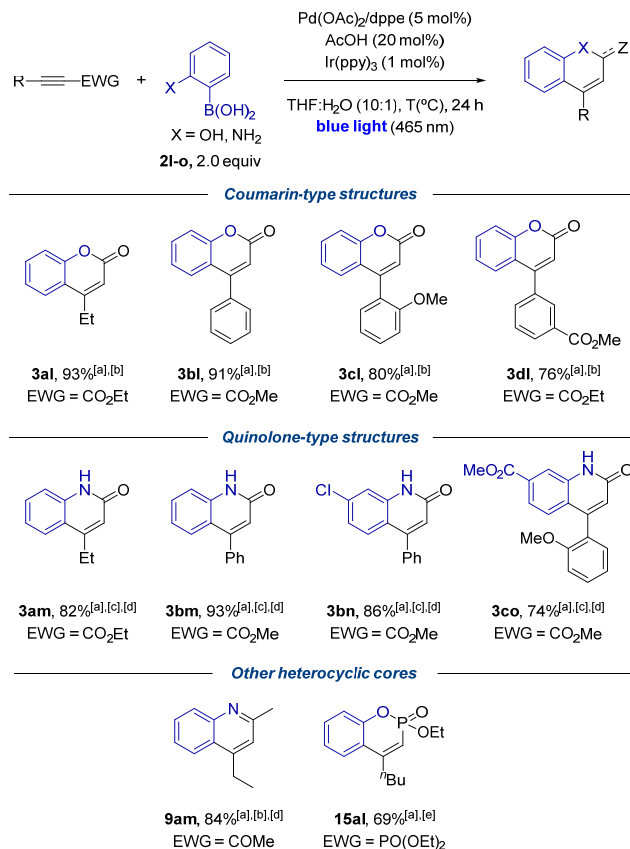
^aDetermined in the reaction crude by ¹H NMR. ^bAfter flash chromatography.

delivered the corresponding *anti*-hydroarylated product with excellent yields (86–94%) and perfect stereoselectivity (>98%). These include mono- and diesters (Z)-**3aa** and (Z)-**5aa**, aldehyde (Z)-**7aa**, ketone (Z)-**9aa**, and amide (Z)-**11aa**. Other EWGs, such as sulfones (SO₂Ph, (Z)-**13aa**) and phosphonates (PO(OEt)₂, (Z)-**15aa**), were also amenable to the transformation (93 and 86% yield, respectively, with complete stereoselectivity).

We next explored the use of different boronic acids and a selection of representative alkynes described above (alkynyl ester **1a**, alkynyl ketone **8a**, alkynyl sulfone **12a**, and alkynyl phosphonate **14a**) in combination with both electron-rich and electron-poor boronic acids (Scheme 3), although we placed special attention on the latter class for the reasons explained in the introduction. We observed that carbonyl-containing conjugated alkynes **1a** and **8a** showed high reactivity and selectivity. Different electron-poor arenes bearing substituents at the *para*- and *meta*- positions of the aryl ring, such as aldehyde ((Z)-**3ab** and (Z)-**9ab**), ketone ((Z)-**3ac** and (Z)-**9ac**), nitro ((Z)-**3ad** and (Z)-**9ad**), and bromo ((Z)-**9ag**) groups, were easily installed. Notably, we did not observe incompatibilities between Pd and the substituents in the aryl rings, and we obtained clean formation of the corresponding olefins in very good yields (74–93%) and excellent *Z*-stereoselectivities (95% in the worst case). This strategy was also amenable to the

Scheme 3. *anti*-Hydroarylation: Arene Scope

^aDetermined by ¹H NMR in the reaction crude. ^bExceptions indicated in each case. ^cAfter flash chromatography.

Scheme 4. Sequential *anti*-Hydroarylation/Cyclization

^aYields after flash chromatography. ^bRoom temperature. ^c60 °C. ^dAddition of Cs₂CO₃ (2 equiv). ^e80 °C, sealed tube.

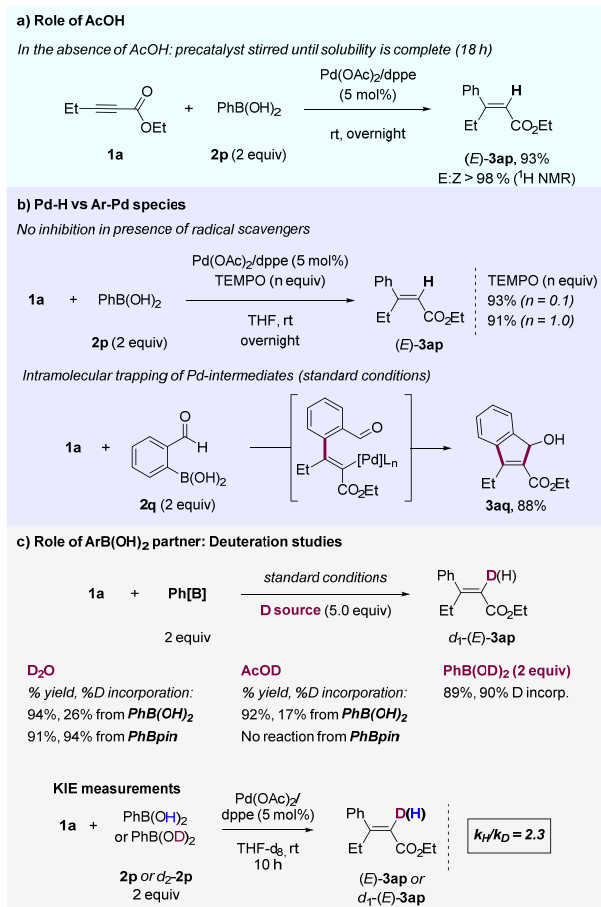
ization of substrates bearing two aryl substituents at the β -position is challenging, and examples of effective methods to achieve this are still scarce,¹⁸ we found that the isomerization/cyclization sequence on diarylated compounds with *ortho*-OH and NH₂ substituents took place in very good yields.¹⁹ This observation supports the existence of a dynamic equilibrium between *E*- and *Z*-olefins, which is shifted irreversibly to the *cis* form by the lactonization/lactamization event.

Various reports have proposed a Pd–H insertion pathway when AcOH is used as a mediator in hydroarylations of alkynes,^{5a,20} which would form by oxidative addition of the acid to Pd(0). However, evidence for a productive hydroarylation pathway involving Pd–H species is inconclusive. For this reason, we performed experiments to shed light on the reaction mechanism and the nature of the Pd intermediates (Scheme 5).

Role of AcOH (Scheme 5a). The difference noted in the experiments using AcOH can be rationalized in terms of solubility of the Pd/dppe complex: formation of a transparent, orange solution of the Pd(OAc)₂/dppe mixture in the presence of the acid, as opposed to formation of a turbid solution in its absence (see the Supporting Information for details). However, even in the absence of AcOH the solution turns transparent when the mixture is stirred for 18 h at room temperature, showing comparable catalytic efficiency (using this solution the (*E*)-3ap was obtained in 93% yield).

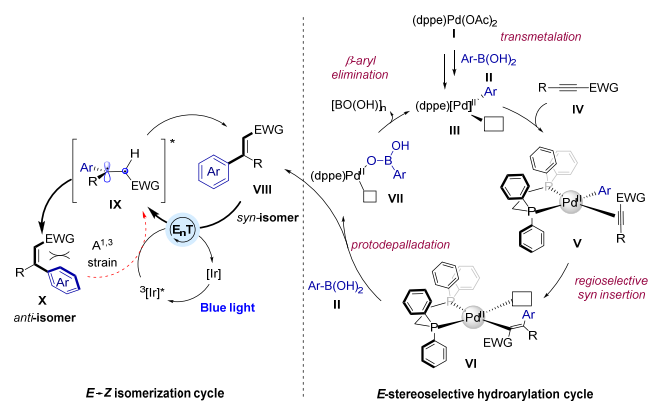
Trapping experiments (Scheme 5b). Previous work by Espinet²¹ described the inhibition of the catalytic activity of Pd–H species by adding radical traps to the reaction media, although alkyl- or aryl–Pd complexes remain unaffected. In our case, the

Scheme 5. Mechanistic Experiments



hydrolysis of the pinacol ester), the hydroarylation product [*d*₁-(E)-3ap] was obtained in 91% yield (94% D, Scheme 5c). Additionally, as expected, the reaction of 1a with PhBpin under the conditions shown in entry 1 of Table 1 resulted in the exclusive recovery of starting material (see Supporting Information). Monitoring the reaction by ¹H NMR using PhB(OH)₂ and PhB(OD)₂ boronic acids allowed us to determine a KIE by independent experiments. The kinetic measurements delivered a non-negligible primary KIE (k_H/k_D = 2.3), which suggests that protodemetalation might be the rate-determining step of the Pd-catalyzed reaction. A mechanistic proposal for this tandem process is outlined in Scheme 6. The

Scheme 6. Plausible Tandem Catalytic Cycle for the Overall anti-Hydroarylation Process



reaction would start with the formation of aryl-Pd species III from Pd(II) precatalyst I and boronic acid II.²² Coordination of alkyne IV to Pd followed by 1,2-insertion into the Ar-Pd bond would yield to the cationic alkenyl-Pd intermediate VI.²³ As deuteration analysis and kinetic measurements suggest, further protodepalladation of VI by II would release the syn-hydroarylated product VIII along with Pd-O-B intermediate VII, which could regenerate the catalytically active Ar-Pd species via β-aryl elimination.²⁴ Subsequently, irradiation of the Ir photocatalyst with blue light (465 nm) would enable the formation of a long-lived ³Ir* that undergoes triplet sensitization of the syn-alkene VIII via an energy transfer (EnT) process.^{11a,f} The corresponding excited alkene IX could evolve into the S₀ of the anti-alkene X upon relaxation. In this situation, the anti-isomer X is much less available for interaction with the photocatalyst due to deconjugation between the aryl group and the C-C double bond because of the A^{1,3} strain, which raises up the triplet state of the alkene.^{11a-c,25} Thus, the anti-isomer accumulates in the photostationary state. This hypothesis is substantiated by Stern-Volmer experiments conducted by Gilmour^{11c,25b} and Weaver.^{11f} This match/mismatch interaction between the triplet state of the photocatalyst and the E- and Z-stereoisomers enables directionality in the stereoselectivity of this reaction.

In conclusion, we have developed a practical catalytic formal anti-hydroarylation of activated internal alkynes. Our method relies on the tandem combination of two catalytic cycles: a Pd-catalyzed hydroarylation and an Ir-photocatalyzed E-Z isomerization. This strategy also provides a solution for the anti-hydroarylation of activated alkynes with electron-poor arenes. Additionally, relevant cores in biologically active derivatives can be prepared from simple alkynes and ortho-substituted boronic acids. Deuteration and trapping experiments suggest that the insertion of Ar-Pd is a likely pathway in the reaction

addition of TEMPO to the reaction between 1a and PhB(OH)₂ had no effect on the reactivity of the system, regardless of the number of equivalents of TEMPO used (>90% yield with either 0.1 or 1 equiv). We reasoned that if an Ar-Pd species were the putative intermediate of the hydroarylation step, the resulting alkenyl-Pd from the 1,2-insertion of the alkyne into the Ar-Pd bond could be trapped in an intramolecular fashion. When boronic acid 2q—with an aldehyde installed at the ortho-position—reacted with 1a, a cyclization product was obtained in 88% yield. This result, explained by reaction of a vinyl-Pd species with a nearby aldehyde, supports the involvement of Ar-Pd species as reaction intermediates. Together, the above observations suggest that Pd-H species are not intrinsically involved in the reaction mechanism and indicate a role of AcOH as a promoter of the solubility of the Pd(OAc)₂/dppe precatalyst.

Role of ArB(OH)₂ (Scheme 5c). First, we performed deuteration studies aimed at determining the source of the H atom in the protodemetalation step. The reaction of 1a in the presence of PhB(OH)₂ and 5 equiv of D₂O under the optimized reaction conditions resulted in 26% D-incorporation at the alkene. Interestingly, the treatment with a more acidic deuterium donor, such as AcOD, led to a lower deuteration of the alkene (17%). However, when the reaction was carried out in the presence of PhB(OD)₂, the incorporation of deuterium was almost complete (90%). These results indicate a dual role of PhB(OH)₂ in the process, as both an aryl and proton donor. In line with this hypothesis, no reaction was observed between 1a and PhBpin when AcOD was used in the absence of water, whereas in the presence of water (which is known to promote

237 mechanism, which is in contrast to previous mechanistic
238 proposals via Pd–H intermediates.

239 ■ ASSOCIATED CONTENT

240 ■ Supporting Information

241 The Supporting Information is available free of charge at
242 <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02281>.

243 Experimental procedures, mechanistic studies, deuteria-
244 tion experiment, kinetic isotope effect, determination of
245 the stereochemistry, and NMR spectra (PDF)

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269 Notes

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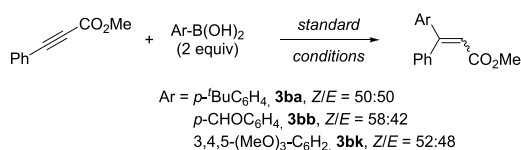
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