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Rh-Catalyzed *Ortho* C−H Alkynylation of Aromatic Aldehydes

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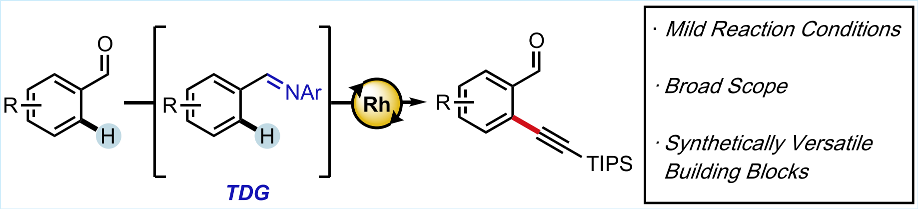


ABSTRACT: The Rh(III)-catalyzed *ortho*-alkynylation of benzaldehydes is enabled by the transient formation of an imine as a directing group. A broad scope of substrates was obtained under mild reaction conditions, granting access to mono- and dialkynylated products. The functionalization of readily available building blocks allowed the development of modular syntheses of dibenzopentalenes, isoquinolines, indoles, and indolines.

Alkynes are among the most versatile functional groups.[1] Recent advances in π-Lewis acid catalysis, in particular gold(I) and platinum(II), has allowed the development of numerous transformations by means of selective activation of alkynes.[2] These advances in methodology have been extensively used as synthetic handles in different annulation reactions, including the construction of polyaromatic hydrocarbons.[3]

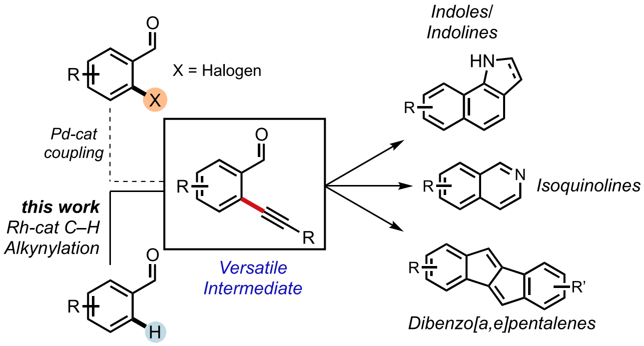
The synthesis of aryl alkynes often relies on the cross-coupling with an aryl halide or triflate.[4] As an alternative, C−H alkynylation provides a powerful tool for the introduction of an alkyne avoiding the use of aryl halides precursors, which could be difficult to access in complex molecular settings. Recently, C−H activation of arenes by electrophilic acetylenes such as EBX or bromo-alkynes have been reported.[5] In our research program on the development of novel methods for the synthesis of alkynes, we investigated the Ru- and Rh-catalyzed *peri*- and *ortho*-alkynylation directed by a variety of functional groups including phenols, acids, esters, ethers, ketones, sulfides, sulfoxides, and amines.[6,7]

Herein, we present the Rh(III)-catalyzed *ortho*-alkynylation of benzaldehydes enabled by the formation of an imine as a transient directing group (TDG) (Scheme 1).[8,9] This method allows accessing alkynes or dialkynes from readily available aromatic aldehydes under mild conditions. The resulting *o*-alkynyl benzaldehydes can be easily converted into polyfunctionalized compounds, such as dibenzopentalenes, isoquinolines, indoles, and indolines, which are important building blocks.

Our studies commenced by exploring the Rh(III)-catalyzed alkynylation of benzaldehydes, under the conditions developed in our group.[6b] However, our initial attempts using 2-methylbenzaldehyde (**1a**) as substrate failed to give the alkynylated product **2a** (Scheme 2). We envisioned that the formation of an imine as the transient directing group using substoichiometric amounts of an aniline would generate a more efficient directing group and enable this transformation.[10] Thus, addition of 15 mol % of aniline to the reaction afforded alkynylated product **2a** in 35% yield. Fine-tuning of the electronic properties of the anilines (**L2**−**L6**) showed that the use of electron-poor 3,5-bis(trifluoromethyl)aniline (**L6**) gave **2a** in 55% yield.

Further studies on the reaction conditions revealed the crucial role of trifluoroacetic acid as an additive, which is hypothesized to promote the formation and hydrolysis of the

Scheme 1. Rh-Catalyzed *Ortho*-Alkynylation of Benzaldehydes



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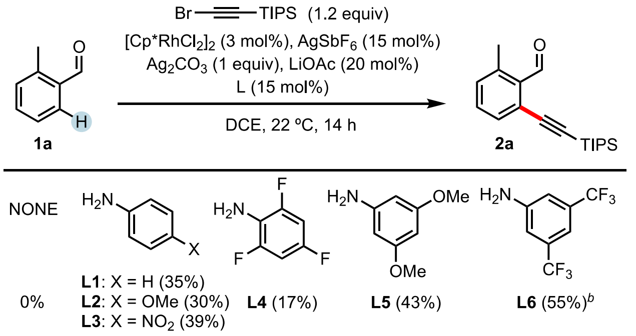
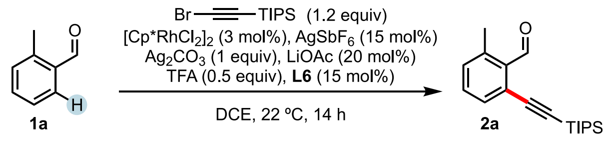
Scheme 2. Aniline Screening in the C−H Alkynylation of 2-Methylbenzaldehyde (1a)[a]



[a]Yields are based on UPLC-MS analysis using biphenyl as internal standard. [b]Yield of the isolated product.

Table 1. Control Experiments on the *Ortho*-Alkynylation of 2-Methylbenzaldehyde (1a)

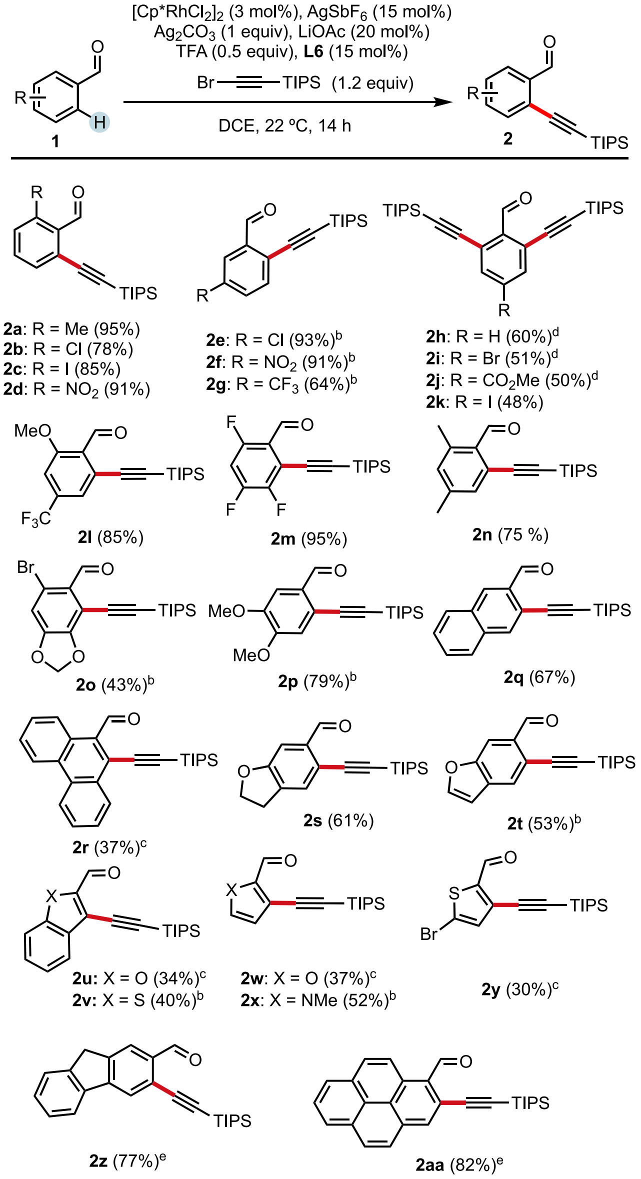


entry	Variation from the standard conditions	yield (%)[a]
1	none	(95)
2	With 0.1 equiv of TFA	28
3	With 5 equiv of TFA	70
4	Without $[Cp^*RhCl_2]_2$	0
5	Without Ag_2CO_3	0
6	Without LiOAc	60
7	Without aniline	0
8	With $MnBr(CO)_5$ or $Cp^*Co(CO)I_2$ or $Pd(OAc)_2$ or $RuCl_2$(*p*-cymene)$]_2$ instead of $[Cp^*RhCl_2]$	0
9	With K_2CO_3 instead of Ag_2CO_3	0
10	With AgOAc, without LiOAc, Ag_2CO_3 and TFA	(88)
11	With $[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	93
12	With 0.5 equiv of H_2O	95

[a]Yield determined by UPLC-MS using biphenyl as internal standard. Yield of the isolated product in parentheses.

imine. Indeed, the addition of 0.5 equiv of TFA increased the yield to 95% (Table 1, entries 1−3). A similar outcome has been observed when AgOAc was used instead of Ag_2CO_3. Control experiments showed the essential role of all reaction components (Table 1, entries 4−7). Other catalysts used in C−H functionalization, such as $MnBr(CO)_5$, $Cp^*Co(CO)I_2$, $Pd(OAc)_2$, or $[RuCl_2(p\text{-cymene})]_2$, were not catalytically competent (Table 1, entry 8). Replacing Ag_2CO_3 by K_2CO_3 (Table 1, entry 9) shuts down the reaction. On the other hand, the replacement of Ag_2CO_3, LiOAc, and TFA with AgOAc (Table 1, entry 10) led to a lower yield. $[Cp^*RhCl_2]_2$ can be replaced by the corresponding iridium catalyst, affording the alkynylated product in similar yield (Table 1, entry 11). Moreover, the presence of water in the reaction mixture does not affect the reaction outcome (Table 1, entry 12).

Scheme 3. Rh-Catalyzed *ortho*-Alkynylation of Benzaldehydes[a]



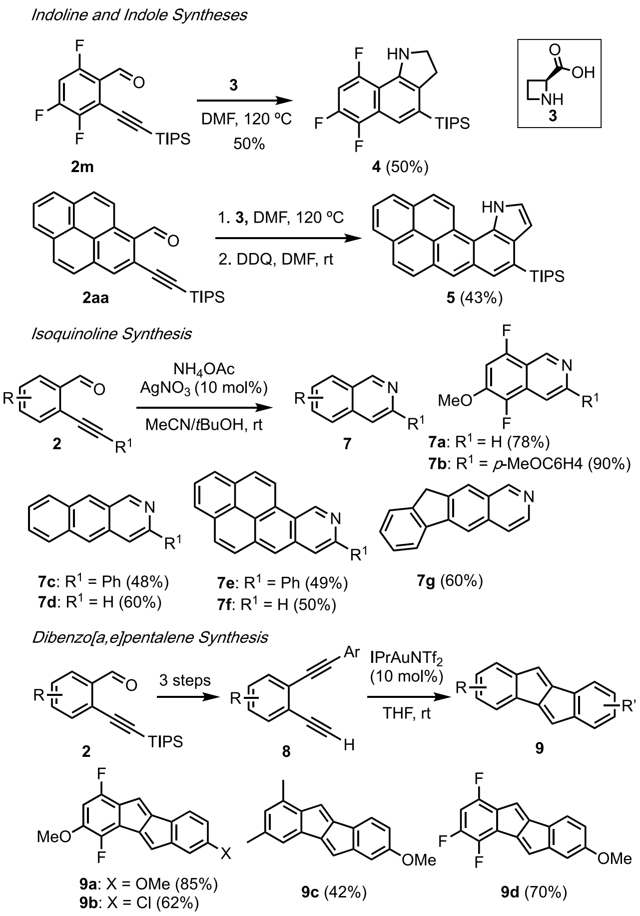
[a]Reaction run on 0.2 mmol scale; yields of the isolated product are shown in parentheses. [b]At 70 °C. [c]With 2 equiv of bromo-alkyne. [d]At 120 °C. [e]With AgOAc (1.2 equiv); without Ag_2CO_3, LiOAc, and TFA.

We next explored the scope of the reaction (Scheme 3). Different substituents, such as halides, nitro, alkyl, ester, acetal, and ether, were tolerated. *Ortho*-, *meta*-, and *para*-substituted benzaldehydes could be alkynylated in 50−95% yield. In the case of *meta*-substituted substrates **2e−g**, the alkynylation occurred selectively as the least hindered position. For *para*-substituted benzaldehydes, the dialkynylated products **2h−k** were obtained selectively using 2 equiv of bromoalkyne. These results not only showcase the efficiency of the catalytic system but also demonstrate the easy access to different *o*,*o*-dialkynylated benzaldehydes, which are important motifs in supramolecular and material sciences.[11]

The alkynylation of polysubstituted benzaldehydes with electron-rich or electron-withdrawing groups was achieved in good to excellent yield. Even electron-rich heterocycles were alkynylated even though high temperatures were required (70−120 °C), yielding the desired ynals **2t−2y** in moderate yield. Polycyclic aromatic compounds reacted smoothly to yield desired compounds **2z** and **2aa** in good yield.

Alkynylbenzaldehydes are versatile building blocks[12] that can be transformed into a variety of products (Scheme 4).

Scheme 4. Synthetic Applications of *o*-Alkynylbenzaldehydes[a,b]

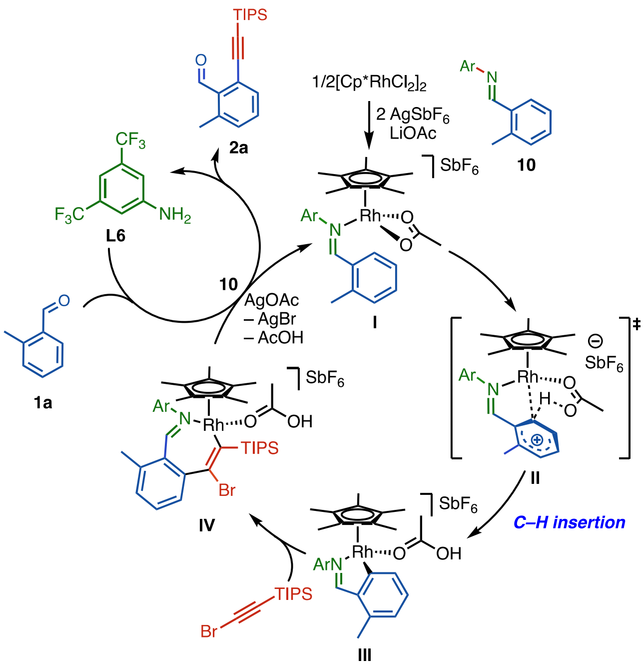


[a]For details on reaction conditions, see Supporting Information. [b]Reaction performed at 80 °C.

Thus, the synthesis of silylated indoline **4** was achieved in one step by the reaction of alkynylbenzaldehyde **2m** with L-azetidine-2-carboxylic acid (**3**),[13] whereas alkyne **2ab** was converted into indole **5** in 43% over two steps. Isoquinolines **7a−f** were readily synthesized by Ag-catalyzed benzannulation.[14]

Finally, we explored the synthesis of dibenzo[*a*,*e*]pentalenes, which are acene-like molecules containing intercalated five-membered rings[15] that have attracted attention because of their potential as organic semiconductors.[16] The properties of these molecules can be fine-tuned by introducing different substituents.[17] Using a three-step procedure, alkynylated products **2**, obtained from benzaldehydes, were easily converted into diynes **8**,[18] which led to dibenzo[*a*,*e*]pentalenes **9a−d** in moderate to good yields by a Au(I)-catalyzed cyclization.[19] The structure of **9d** was confirmed by X-ray diffraction.[18]

Scheme 5. Proposed Mechanism of the *Ortho*-Alkynylation of Benzaldehydes



The proposed mechanism of the *ortho*-alkynylation of benzaldehydes (Scheme 5) commences with the formation of active catalyst **I** by silver-mediated chloride abstraction of $[Cp^*RhCl_2]_2$, followed by coordination of imine **26** and acetate. C−H activation of complex **I** through transition state **II**[6b,11] leads to cyclometalated rhodium complex **III**, which undergoes insertion into TIPS-bromoalkyne to form seven-membered rhodacycle **IV**. Finally, silver-mediated elimination of the bromide forms the alkynyl imine **10**, which upon hydrolysis affords alkyne product **2a**. We hypothesized that AgOAc and silver trifluoroacetate have a crucial role in the imine formation and hydrolysis, promoting the turnover of the catalytic cycle. The rhodium catalytic cycle is then closed by coordination of imine **10**, formed by the condensation of aniline **L6** and aldehyde.[9,20]

In conclusion, we report the development of a Rh(III)-catalyzed *ortho*-alkynylation, enabled by the formation of an imine as a TDG by reaction with substoichiometric amounts of an aniline. This synthetic method allows alkynylating a broad scope of benzaldehydes and other aromatic aldehydes, offering an orthogonal approach to traditional cross-coupling reaction. Furthermore, the resulting products are versatile intermediates to access a variety of polyaromatic compounds. We envision that this method will be of interest for the preparation of many building blocks as well as for late-stage functionalization, considering the mild conditions used and the broad compatibility with many functional groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04243.

Experimental procedures and characterization data for compounds (PDF)

Accession Codes

CCDC 2050996 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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