

Rhodium-catalyzed arylyative cyclization of alkynyl malonates by 1,4-rhodium(I) migration†

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The synthesis of functionalized 1-tetralones by the rhodium(I)-catalyzed reaction of alkynyl malonates with arylboronic acids is described. These arylyative cyclizations proceed via an alkenyl-to-aryl 1,4-Rh(I) migration as a key step. Preliminary results of an enantioselective variant of these reactions are also presented.

Domino reactions that consist of a metal-catalyzed addition of an aryl nucleophile to an alkyne, followed by an intramolecular nucleophilic addition of the resulting alkenylmetal species onto a tethered electrophile, are versatile transformations for the preparation of hetero- and carbocyclic products.¹ A variation of these arylyative cyclizations involves the 1,4-migration of the metal² from the initially formed alkenylmetal species **A** onto an aryl site, followed by cyclization of the resulting arylmetal species **B** onto the electrophile (Scheme 1A). This through-space transmission of reactivity further increases the synthetic capabilities of arylyative cyclizations, and to date, reactions based upon alkenyl-to-aryl 1,4-

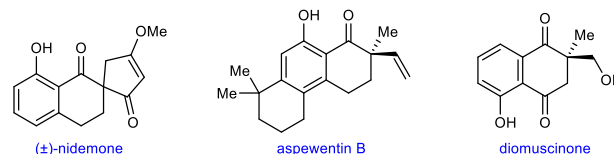
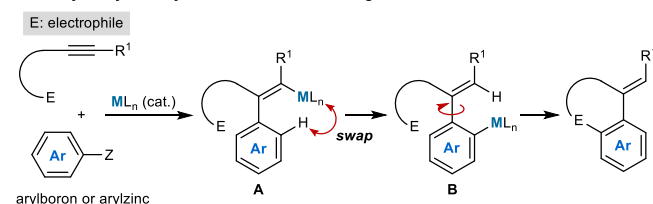


Fig 1 Natural products containing a 1-tetralone with an all-carbon quaternary stereocenter at C2

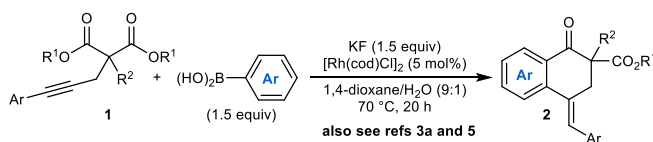
migrations of rhodium,³ iridium,⁴ and cobalt⁵ have been described.^{6,7,8,9,10,11} The use of esters as the electrophiles in these reactions leads to the formation of aromatic ketones. In this context, the Murakami^{3a} and Yoshikai⁵ groups have shown that alkyne-tethered esters react with arylboron and arylzinc reagents in arylyative cyclizations under rhodium and cobalt catalysis, respectively. However, only symmetrical alkynes were employed in these studies.^{3a,5} Although this feature eliminates the challenge of controlling regioselectivity in the initial arylmetalation, it does limit synthetic utility. Here, we describe the rhodium-catalyzed reaction of arylboronic acids with alkynyl malonates **1**, in which the alkyne is unsymmetrically substituted (Scheme 1B). These arylyative cyclizations produce 1-tetralones containing an all-carbon quaternary stereocenter at C2, a structural motif that appears in several natural products such as (±)-nidemone,¹² aspewentin B,¹³ and diomuscione¹⁴ (Figure 1). Preliminary results of an enantioselective variant are also described.

It is known that carbometalation of alkynes substituted with one alkyl and one aryl group are often highly regioselective.¹⁵ Accordingly, bis(2,2,2-trifluoroethyl)malonate **1a**, which contains such an alkyne, was selected for our initial experiments in the hope that a highly regioselective synthesis of 1-tetralones by arylyative cyclization could be achieved. First, a mixture of **1a** and PhB(OH)₂ (1.5 equiv) was heated at 70 °C for 20 h in the presence of 5 mol% of [Rh(cod)Cl]₂ and various bases (1.5 equiv) (Table 1).¹⁶ We were pleased to observe that arylyative cyclization was successful and the best results were obtained using KF as the base in 1,4-dioxane/H₂O (9:1) as the solvent, which gave 1-tetralone **2aa** in 75% yield as determined by ¹H NMR analysis of the crude mixture using 1,4-dimethoxybenzene as an internal standard (entry 1). This experiment also gave alkyne hydroarylation product **3ab** in 14% yield. Changing the quantity of H₂O in the reaction medium by using anhydrous

A. Catalytic arylyative cyclizations via 1,4-metal migration



B. Rh(I)-catalyzed synthesis of tetralones by arylyative cyclization (this work)

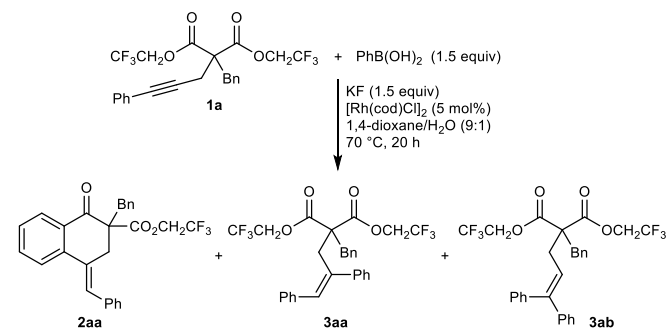


Scheme 1 Catalytic arylyative cyclizations via 1,4-metal migration

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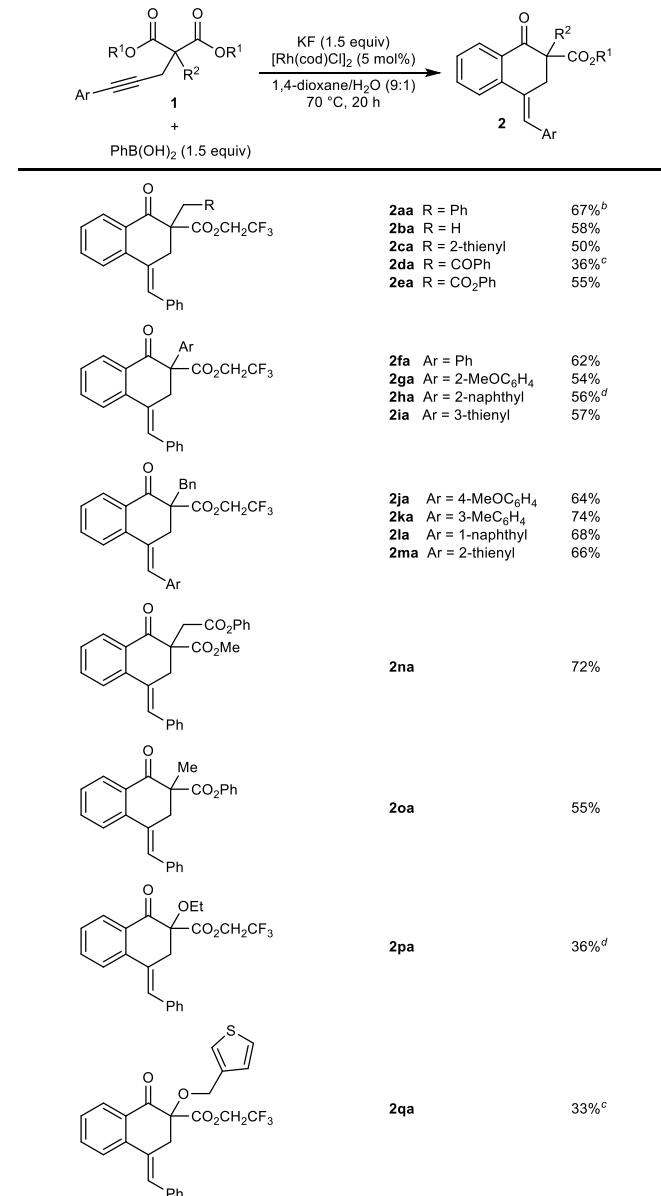
Table 1 Evaluation of reaction conditions^a

| Entry | Deviation from standard conditions | Yield of 2aa (%) ^b | Yield of 3aa (%) ^b | Yield of 3ab (%) ^b |
|-------|---|--------------------------------------|--------------------------------------|--------------------------------------|
| 1 | None | 75 | — | 14 |
| 2 | 1,4-Dioxane as solvent | 42 | 19 | 14 |
| 3 | In 1,4-dioxane/ H_2O (4:1) | 54 | 5 | 9 |
| 4 | Toluene as solvent | 28 | 28 | 14 |
| 5 | Xylenes as solvent | 33 | 42 | 14 |
| 6 | Et_3N instead of KF | 47 | 19 | 14 |
| 7 | Cs_2CO_3 instead of KF | 56 | — | 9 |

^a Reactions were conducted with 0.05 mmol of **1a**. ^b Determined by ^1H NMR analysis of the crude reactions using 1,4-dimethoxybenzene as an internal standard.

1,4-dioxane or 1,4-dioxane/ H_2O (4:1) gave lower yields of **2aa** along with significant quantities of alkyne hydroarylation products **3aa** and **3ab** (entries 2 and 3). Other solvents such as toluene (entry 4) and xylenes (entry 5) also gave inferior results. Other bases such as Et_3N (entry 6) and Cs_2CO_3 (entry 7) are also effective but the yields of **2aa** are appreciably lower compared with using KF (entry 1). The conditions shown in entry 1 were therefore selected for use in further experiments.

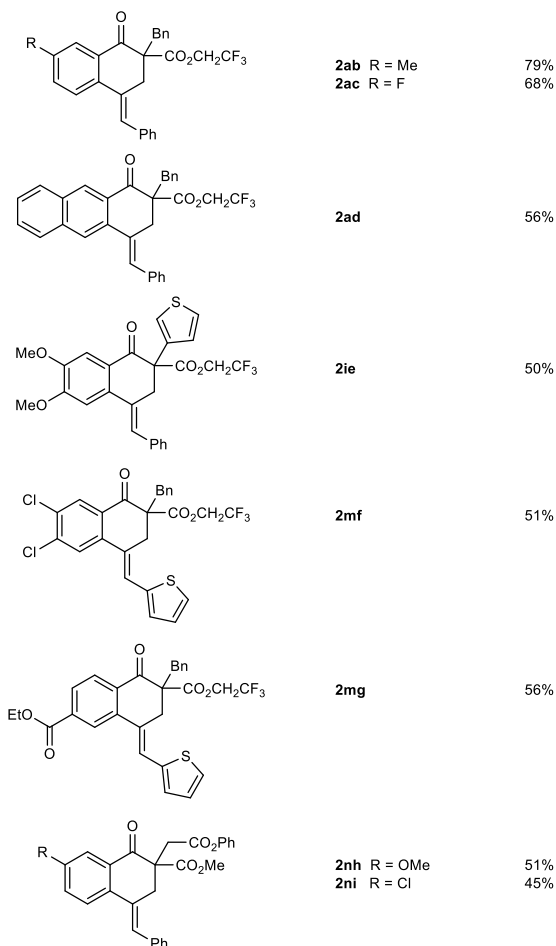
The scope of this reaction with respect to the alkynyl malonate was then examined in reactions with PhB(OH)_2 , which gave 1-tetralones **2aa–2qa** in 33–74% yield (Table 2). In some cases (**2ha** and **2pa**), it proved beneficial to increase the loading of $[\text{Rh(cod)Cl}]_2$ to 10 mol% and the quantity of PhB(OH)_2 to 2.0 equivalents. The reaction producing **2aa** also gave a 1:1.25 mixture of inseparable alkyne hydroarylation products **3aa** and **3ab** (see Table 1 for the structures), respectively, in 19% combined yield. Alkyne hydroarylation products corresponding to **3aa** and **3ab** were not isolated in subsequent experiments using other substrates. The reaction is tolerant of a wide range of carbon-linked substituents at the 2-position of the substrate, including benzyl (**2aa** and **2ja–2ma**), methyl (**2ba** and **2oa**), 2-thienylmethyl (**2ca**), 2-oxo-2-phenylethyl (**2da**), 2-oxo-2-phenoxyethyl (**2ea**¹⁷ and **2na**), phenyl (**2fa**), 2-methoxyphenyl (**2ga**), 2-naphthyl (**2ha**), and 3-thienyl (**2ia**) groups. Heteroatom substituents at the 2-position are also accommodated, such as ethoxy (**2pa**) and 3-thienylmethoxy (**2qa**) groups. The alkynyl substituent can be changed from a phenyl group (**2aa–2ia** and **2na–2qa**) to 4-methoxyphenyl (**2ja**), 3-methylphenyl (**2ka**), 1-naphthyl (**2la**), and 2-thienyl (**2ma**) groups. A substrate with a methyl-substituted alkyne did undergo arylative cyclization in low yield but the product **2ra** contained unidentified, inseparable impurities.¹⁸ In addition, a substrate containing a terminal alkyne gave only a complex mixture of unidentified products. Pleasingly, the reaction is not limited to bis(2,2,2-trifluoroethyl) malonates;

Table 2 Scope with respect to the alkynyl malonate^a

^a Reactions were conducted with 0.30 mmol of **1a–1q** in 3 mL of 1,4-dioxane/ H_2O (9:1). Yields are of isolated products. ^b This experiment also gave a 1:1.25 inseparable mixture of **3aa** and **3ab**, respectively, in 19% combined yield. ^c The reaction time was 24 h. ^d Conducted using 10 mol% of $[\text{Rh(cod)Cl}]_2$ and 2.0 equiv of PhB(OH)_2 .

substrates containing dimethyl or diphenyl malonates gave 1-tetralones **2na** and **2oa** in 55% and 72% yield, respectively.

Table 3 presents the results of the reactions of representative substrates **1a**, **1i**, **1m**, and **1n** with various arylboronic acids, which gave 1-tetralones **2ab–2nj** in 45–79% yield. The arylboronic acid scope includes a range of *para*- (**2ab**, **2ac**, **2nh**, and **2ni**), *meta*- (**2mg**), and disubstituted phenylboronic acids (**2ie** and **2mf**) containing methyl (**2ab**), halide (**2ac**, **2mf**, and **2ni**), carboethoxy (**2mg**), or alkoxy groups (**2ge** and **2nh**). 2-Naphthylboronic acid (**2ad**) is also tolerated. In the case of 2-naphthylboronic acid and 3-ethoxycarbonylphenylboronic acid, 1,4-Rh(I) migration occurred to the sterically more accessible position (**2ad** and **2mg**, respectively). 3-Thienylboronic acid also reacted successfully with **1a**; however,



Reaction scheme (1) showing the synthesis of **2aj** and **2ai'** from **1a** and 2-thienylboronic acid.

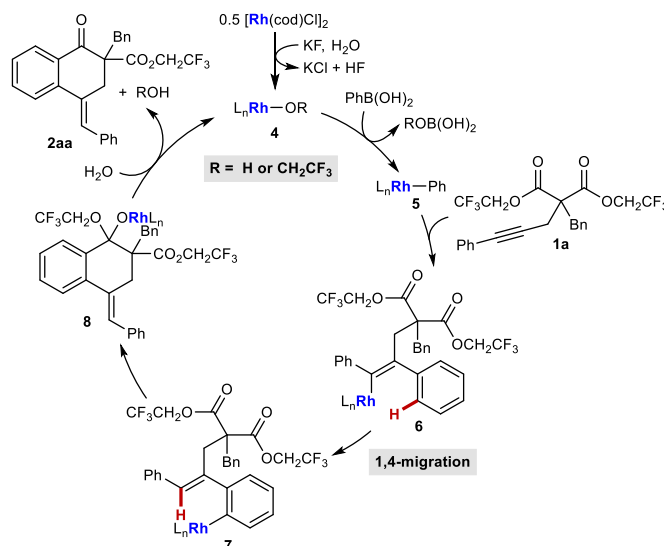
Reaction conditions:

- KF (1.5 equiv)
- [Rh(cod)Cl]₂ (5 mol %)
- 1,4-dioxane/H₂O (9:1)
- 70 °C, 20 h

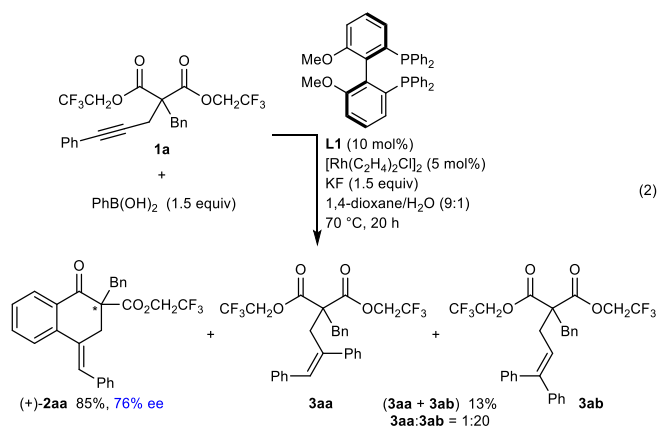
Yields:

- 2aj**: 21%
- 2ai'**: 42%

generate rhodium hydroxide **4** (R = H), which can undergo transmetalation with $\text{PhB}(\text{OH})_2$ to give arylrhodium species **5**. Phenylrhodation of the alkyne of **1a** gives alkenylrhodium species **6**, which then undergoes alkenyl-to-aryl 1,4-Rh(I) migration to give arylrhodium species **7**. Cyclization of **7** by 1,2-addition onto one of the esters produces rhodium alkoxide **8**, which collapses to release the product **2aa** and regenerate the active rhodium complex **4** (which could have a either a trifluoroethoxide or hydroxide counterion).



Finally, preliminary efforts at developing an enantioselective variant of this reaction were conducted. After some experimentation,¹⁹ heating **1a** with PhB(OH)₂ (1.5 equiv) in the presence of [Rh(C₂H₄)₂Cl]₂ (5 mol%), (*R*)-MeO-BIHEP (**L1**, 10 mol%), and KF (1.5 equiv) in 1,4-dioxane/H₂O (9:1) at 70 °C gave (+)-**2aa** in 85% yield and 76% ee, along with an inseparable mixture of **3aa** and **3ab** in 13% yield (eqn (2)).



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new domino reactions involving 1,4-metal migration are ongoing and will be reported in due course.²⁰

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- The structure of **2ea** was further confirmed by X-ray crystallography. CCDC 1938497†.
- See the Supplementary Information for further details.
- For further details about the evaluation of chiral ligands in these reactions, see the Supplementary Information.
- The research data associated with this publication can be found at DOI: 10.17639/nott.7008