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**ARTICLE** *in* CHEMISTRY - A EUROPEAN JOURNAL · JUNE 2013

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# Synthesis of Fluorine-Containing Multisubstituted Phenanthridines by Rhodium-Catalyzed Alkyne [2+2+2] Cycloaddition and Tandem $sp^2$ C–H Difluoromethylenation

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**Abstract:** A highly efficient method for the synthesis of fluorine-containing multisubstituted phenanthridines through Rh-catalyzed alkyne [2+2+2] cycloaddition reactions has been developed. This method exhibits excellent functional-group compatibility. When a bromodifluoromethyl group, rather than a trifluoromethyl group, was employed in the cycloaddition reaction, more-complicated polycyclic compounds were obtained through tandem Rh-catalyzed cycloaddition/C–H difluoromethylenation. This route provides convenient access to fluorine-containing polycyclic compounds.

**Keywords:** cycloaddition · fluorine · homogeneous catalysis · polycycles · rhodium

## Introduction

Since the seminal study by Reppe et al., transition-metal-catalyzed alkyne [2+2+2] cycloaddition reactions have become a powerful tool for the construction of substituted aromatic and nonaromatic cyclic compounds.[1] Compared with other remarkable reactions that are catalyzed by transition metals, such as cross-coupling reactions, these ring-forming reactions could be able to accomplish the required chemistry in a single step, rather than through tedious and low-yielding multistep strategies.[2]

A large number of such cycloaddition reactions with a variety of transition metals, such as Co, Ni, Pd, Rh, Ru, Ir, Fe, Zr, Cr, Ti, etc., have been well-documented.[3] Under optimized conditions, a broad range of substituted cyclic molecules, such as benzenes, pyridines, pyridones, 1,3-cyclohexadienes, pyrones, and pyrans, can be obtained from various unsaturated substrates, such as alkynes, nitriles, isocyanates, alkenes, carbon dioxide, aldehydes, and ketones.[4] Moreover, typically, no extra base or acid is required to facilitate these reactions. Thus, a wide range of functional groups, such as esters, ketones, amides, nitriles, alcohols, amines, halogens, and even sulfides, can be well-tolerated.[5]

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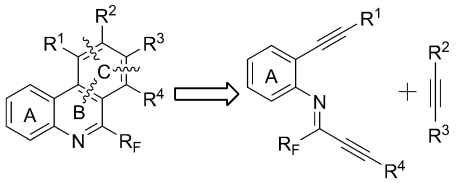
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300288.

Given these above-mentioned advantages, [2+2+2] cycloaddition reactions are not only useful for constructing simple cyclic compounds but they are also a good method for the assembly of more-complicated and challenging compounds. For example, Tanaka et al. have reported the synthesis of enantioenriched [9]helicene-like molecules through double [2+2+2] cycloaddition reactions,[6] Shibata et al. have reported the enantioselective synthesis of chiral tripodal cage compounds through the [2+2+2] cycloaddition of branched triynes,[7] and Witulski and Alayrac have reported the synthesis of fused carbazoles by alkyne cyclotrimerization reactions.[8]

Phenanthridines are important core structures in a large class of compounds, including many significant natural products, biologically and therapeutically active compounds, and functional materials.[9] Thus, numerous different strategies for the construction of phenanthridines have been explored.[10] Meanwhile, the incorporation of fluorine moieties into the phenanthridine motif could lead to great changes in its properties, such as its conformation, solubility, lipophilicity, metabolic stability, hydrogen-bonding ability, and chemical reactivity.[11] However, methods for introducing fluorine atom(s) into phenanthridines are still scarce. Herein, we report a new method for the synthesis of fluorine-containing phenanthridines by using an alkyne [2+2+2] cycloaddition strategy.

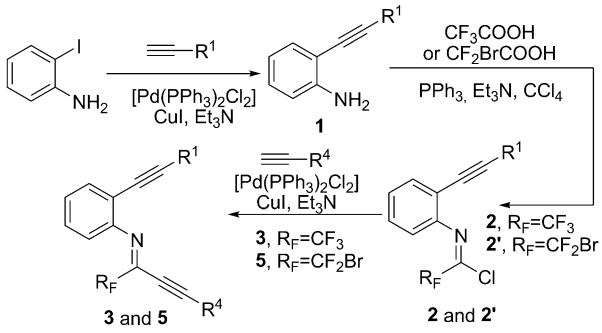
## Results and Discussion

Based on our recent work on the synthesis of fluorine-containing alkynylimines,[12] we envisioned a strategy that involved [2+2+2] cycloaddition reactions between diynes **3** or **5** and various alkynes for the synthesis of fluorine-containing phenanthridines (Scheme 1). Diynes **3** and **5** were prepared in three steps starting from commercially available 2-



Scheme 1. Strategy for the A→ABC ring formation.

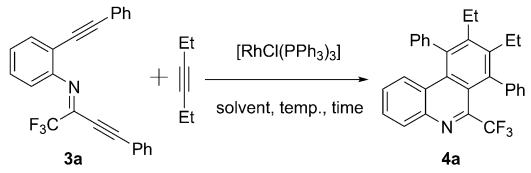
iodoaniline (Scheme 2). After Sonogashira reactions between terminal alkynes and 2-iodoaniline, intermediates **1** were treated with trifluoroacetic acid or bromodifluoroacetic acid under certain conditions to form intermediates **2**.[13] Then, intermediates **2** underwent Sonogashira reactions to give diynes **3** and **5** in good overall yields.[12b]



Scheme 2. Synthesis of cycloaddition precursors **3** and **5**.

Initial studies were focused on the Rh-catalyzed [2+2+2] cycloaddition reaction between diyne **3a** and 3-hexyne. The reaction was optimized with respect to the solvent, temperature, time, and catalyst loading. As shown in Table 1, in the presence of 10 mol% $[RhCl(PPh_3)_3]$, this reaction was smoothly completed in toluene at 90°C within 1 h (Table 1, entry 1). However, when performed at 60°C, the reaction was rather slow and required 12 h to obtain high conversion (Table 1, entry 2).[14] The catalyst loading seemed to have minimal influence on the reaction yield (Table 1, entries 1, 3, 6, and 7) and the reaction could go completion within 8 h, even in the presence of 1 mol% catalyst (Table 1, entry 7). Polar solvents, such as DMF and THF, were also appropriate solvents for this transformation (Table 1, entries 4 and 5). Finally, the optimized conditions were ascertained to be 5 mol% $[RhCl(PPh_3)_3]$ in toluene at 90°C under a nitrogen atmosphere.

Table 1. Optimization of the [2+2+2] cycloaddition reaction catalyzed by Wilkinson's catalyst.[a]

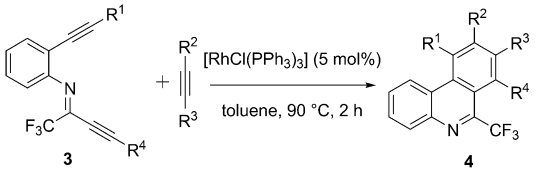


| | Catalyst [mol%] | Solvent | $T$ [°C] | $t$ [h] | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | 10 | toluene | 90 | 1 | 92 |
| 2 | 10 | toluene | 60 | 12 | 93 |
| 3 | 5 | toluene | 90 | 2 | 96 |
| 4 | 5 | DMF | 90 | 2 | 90 |
| 5 | 5 | THF | 70 | 2 | 89 |
| 6 | 2.5 | toluene | 90 | 5 | 92 |
| 7 | 1 | toluene | 90 | 8 | 93 |

[a] General conditions: Diyne **3a**, 3-hexyne (2 equiv), $[RhCl(PPh_3)_3]$, solvent. [b] Yield of isolated product.

To investigate the scope and limitations of this method, we treated various diynes with 3-hexyne as the electrophile partner. When $R^1$ was a phenyl ring and $R^4$ represented another aromatic moiety, both electron-donating groups and electron-withdrawing groups on the aromatic ring had a negligible effect on the transformations, thus giving their corresponding products in excellent yields (Table 2). These data indicate that this reaction has good functional-group tolerance (Table 2, entries 1–7). In addition, when $R^4$ was an aliphatic group, the reaction could also proceed smoothly, thus offering the corresponding phenanthridines in about 90% yield (Table 2, entries 8 and 9). When both $R^1$ and $R^4$ were aliphatic chains, the yields of the corresponding products decreased slightly (Table 2, entries 10 and 11). When $R^1$ was a trimethylsilyl group, the corresponding cycloaddition product could also be obtained, albeit as the desilylated product in a relatively low yield (Table 2, entry 12). Finally, we focused our attention on the electrophile partner. Whereas electron-neutral alkynes, such as diphenylacetylene (Table 2, entry 13), and electron-rich alkynes, such as 2-butyne-1,4-

Table 2. Substrate scope of the [2+2+2] cycloaddition reaction.[a]



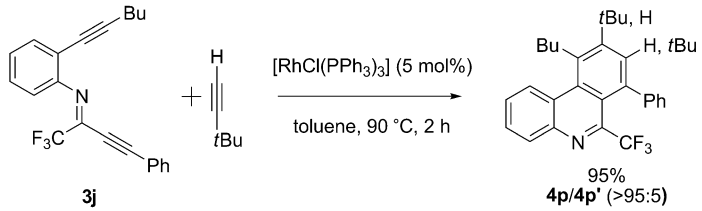
| | $R^1$ | $R^4$ | $R^2$ and $R^3$ | Product | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | Et | **4a** | 96 |
| 2 | Ph | *p*-$OMeC_6H_4$ | Et | **4b** | 88 |
| 3 | Ph | *p*-$ClC_6H_4$ | Et | **4c** | 85 |
| 4 | Ph | *p*-$FC_6H_4$ | Et | **4d** | 90 |
| 5 | Ph | *o*-$ClC_6H_4$ | Et | **4e** | 92 |
| 6 | Ph | *p*-$NO_2C_6H_4$ | Et | **4f** | 85 |
| 7 | Ph | 2-thienyl | Et | **4g** | 96 |
| 8 | Ph | *t*Bu | Et | **4h** | 89 |
| 9 | Ph | Bu | Et | **4i** | 92 |
| 10 | Bu | Ph | Et | **4j** | 88 |
| 11 | Bu | Bu | Et | **4k** | 72 |
| 12[c] | H | Ph | Et | **4l** | 48 |
| 13 | Ph | Ph | Ph | **4m** | 95 |
| 14 | Ph | Ph | $CH_2OH$ | **4n** | 98 |
| 15 | Ph | Ph | $CO_2Me$ | **4o** | 37 |

[a] General conditions: Diyne **3**, alkyne (2 equiv), $[RhCl(PPh_3)_3]$ (5 mol%), toluene, 90°C. [b] Yield of isolated product. [c] The $R^1$ group in starting material **3l** was a trimethylsilyl group.

diol (Table 2, entry 14), efficiently underwent the cycloaddition reaction, electron-deficient alkynes, such as dimethyl acetylenedicarboxylate (DMAD), were not good electrophiles for this transformation (Table 2, entry 15).[15]

Regioselectivity is an important issue in the reactions between diynes and asymmetric alkynes.[16] To test the regioselectivity of this catalytic system, the reaction between compound **3j** and 3-3-dimethyl-1-butyne was carried out. In agreement with previous reports, excellent regioselectivity (>95:5) was observed when bulky groups were involved [Eq. (1)].[16]




(1)

To our surprise, when the trifluoromethyl group on the diynes was replaced by a bromodifluoromethyl group, the reaction of diyne **5a** with 3-hexyne not only gave the desired product (**6a**), but also afforded compound **7a** [Eq. (2)], as confirmed by X-ray crystallography (Figure 1).[17] This unexpected result implies a facile pathway for the construction of more-complicated polycyclic compounds.

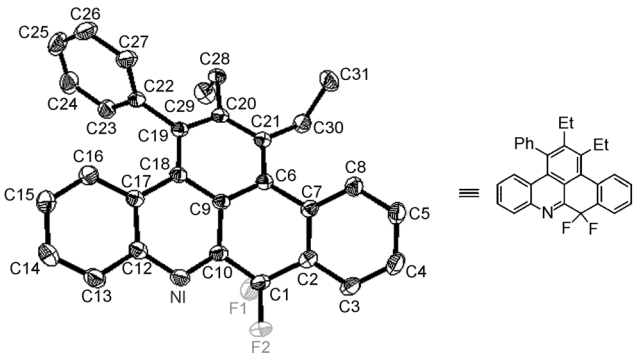
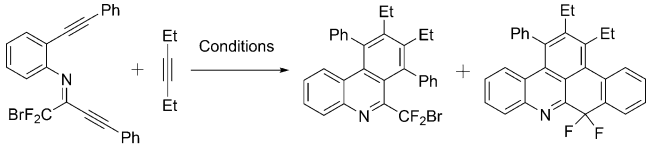



Figure 1. Single-crystal X-ray structure ORTEP diagram of compound **7a**. Hydrogen atoms have been omitted for clarity and the thermal ellipsoids are set at the 30% probability level.

Recently, we have reported a Rh-catalyzed intramolecular coupling reaction that involved a bromodifluoromethyl group.[18] Encouraged by these above-mentioned results, we became interested in developing a tandem cycloaddition/C–H functionalization strategy to directly construct phenanthridines (**7**) from diynes (**5**) as the starting substrates. The reaction conditions were then optimized. First, we mixed substrate **5a** with 3-hexyne, 5 mol% [$RhCl(PPh_3)_3$], and 1 equivalent of $Ag_2CO_3$ in toluene or 1,4-dioxane at 90 °C or 120 °C (Table 3). However, these reactions gave compound **6a** as the major product (Table 3, entry 1–3). Because the alkyne [2+2+2] cycloaddition reaction didn't require the assistance of $Ag_2CO_3$, $Ag_2CO_3$ was added as an additive after the completion of the alkyne [2+2+2] cycloaddition reaction. Unfortunately, a similar result was obtained (Table 3, entry 4). These results imply that the catalyst might lose its activity during the reaction. Thus, another portion of the catalyst was added to the reaction system along with the silver reagent during the second stage. Gratifyingly, the reaction exclusively afforded the desired product (**7a**) in

Table 3. Optimization of the cascade reaction catalyzed by Wilkinson's catalyst.

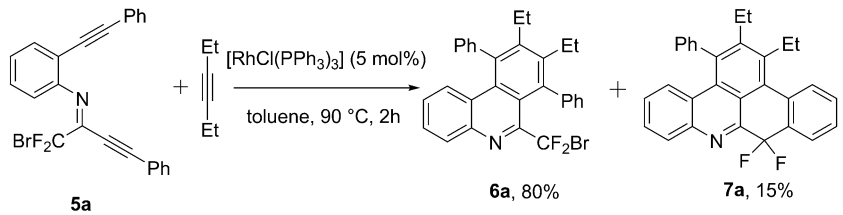



| | Conditions | Yield **6a** [%] | Yield **7a** [%] |
|---|---|---|---|
| 1 | [$RhCl(PPh_3)_3$], $Ag_2CO_3$, toluene, 90 °C | 80 | 16 |
| 2 | [$RhCl(PPh_3)_3$], $Ag_2CO_3$, 1,4-dioxane, 100 °C | 76 | 18 |
| 3 | [$RhCl(PPh_3)_3$], $Ag_2CO_3$, 1,4-dioxane, 120 °C | 73 | 19 |
| 4 | 1) [$RhCl(PPh_3)_3$], 1,4-dioxane, 90 °C<br>2) $Ag_2CO_3$, 120 °C | 66 | 22 |
| 5 | 1) [$RhCl(PPh_3)_3$], toluene, 90 °C<br>2) [$RhCl(PPh_3)_3$], $Ag_2CO_3$, 120 °C | 0 | 75 |
| 6 | 1) [$RhCl(PPh_3)_3$], 1,4-dioxane, 90 °C<br>2) [$RhCl(PPh_3)_3$], $Ag_2CO_3$, 120 °C | 0 | 79 |
| 7 | 1) [$RhCl(PPh_3)_3$], toluene, 90 °C<br>2) [$RhCl(PPh_3)_3$], $Ag_2CO_3$, 1,4-dioxane, 115 °C | 0 | 90 (85)[a] |

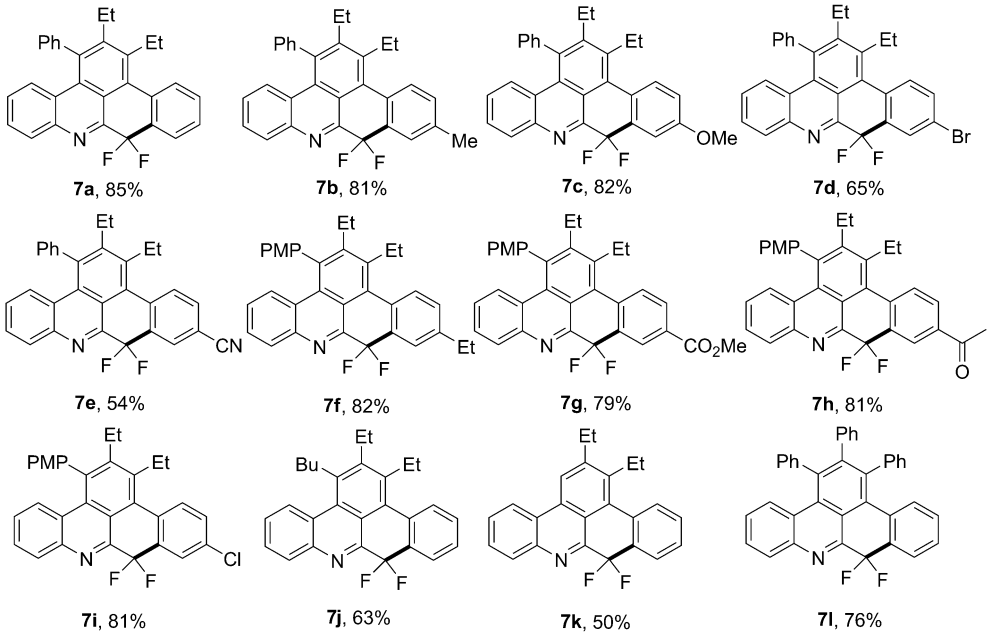
[a] Yield of the isolated product is given in parentheses.

75% yield (Table 3, entry 5). Finally, we identified the optimal reaction conditions after several attempts. During the first stage, the diynes reacted with 3-hexyne in toluene at 90 °C in the presence of 5 mol% [$RhCl(PPh_3)_3$] to form intermediates **6**. During the second stage, 1 equivalent of $Ag_2CO_3$, a second portion of [$RhCl(PPh_3)_3$] (5 mol%), and 1,4-dioxane were added to the reaction mixture. After 4 h at 115 °C, the reaction gave product **7a** in 90% yield (Table 3, entry 7).

As summarized in Scheme 3, a range of phenanthridines that contained electron-donating or electron-withdrawing groups were formed in moderate-to-high yields. These reac-



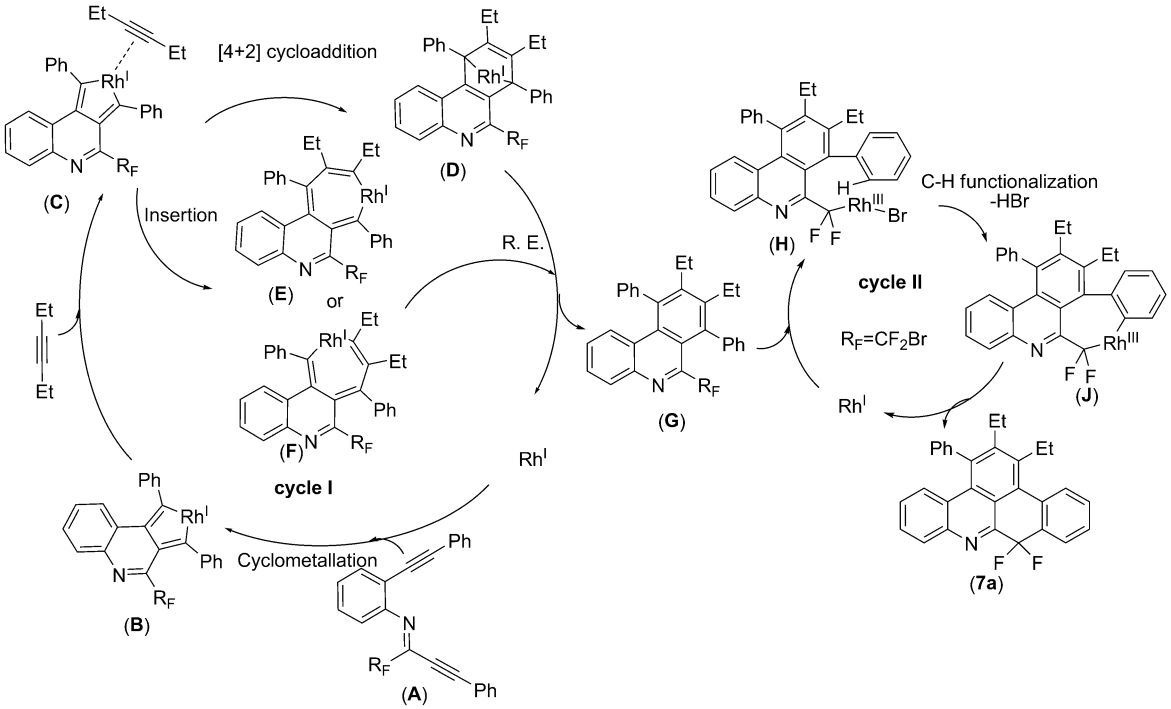

(2)




Scheme 3. One-pot synthesis of polycyclic compounds **7**.

tions are compatible with a number of functional groups, including halogen (**7d** and **7i**), ester (**7g**), ketone (**7h**), and even cyano groups (**7e**). It is well-known that the cyano group could participate in [2+2+2] cycloaddition reactions, which would disturb the outcome of the product.[3,5] However, we didn't identify any other product apart from the desired product, which was obtained in moderate yield. Diynes that were connected with an aliphatic chain or a hydrogen atom could also give the corresponding products (**7j** and **7k**) in moderate yields. Moreover, other alkynes, such as diphenylacetylene, could also be used as the reaction partner (**7l**).

Based on our preliminary data, we propose a plausible reaction mechanism, as shown in Scheme 4. Cycle I shows the




Scheme 4. Proposed mechanism for the formation of phenanthridines **4** and **7**.

mechanism of the alkyne [2+2+2] cycloaddition reaction and cycle II shows the mechanism of the C–H difluoromethylenation step. Diyne **A** undergoes cyclometalation with $Rh^{I}$ to form intermediate **B**, which then coordinates with the alkyne to give intermediate **C**. Then, addition or insertion of the alkyne to metallacycle **C** occurs to give intermediates **D**, **E**, or **F**. The phenanthridine product is formed upon reductive elimination of the metal. When the bromodifluoromethyl group, rather than the trifluoromethyl group, is involved in the reaction, according to our previous results,[18] intermediate **G** (cycle II) undergoes oxidative addition to form intermediate **H**. This latter species undergoes C–H functionalization to give intermediate **J**. Reductive elimination then generates the product (**7a**).

## Conclusion

In conclusion, we have developed a highly efficient method for the construction of fluorine-containing multisubstituted phenanthridines through Rh-catalyzed diyne [2+2+2] cycloaddition reactions. This new method offers the mild and direct synthesis of multisubstituted phenanthridines with good functional-group tolerance. Moreover, excellent regioselectivity in this reaction was obtained when bulky groups were employed. With substrates that contained bromodifluoromethyl groups, more-complicated polycyclic compounds were obtained through a tandem Rh-catalyzed cycloaddition/C–H difluoromethylenation process, which might be useful in constructing polycyclic fluorine-containing compounds.

## Experimental Section

**General procedure for the synthesis of compound 4**: Diyne **3** (0.2 mmol), the alkyne (2 equiv), and Wilkinson's catalyst were stirred together in toluene (2 mL) at 90 °C under a nitrogen atmosphere. After the reaction was complete (by TLC), the volatile compounds were removed in vacuo and the crude residue was purified by column chromatography on silica gel (EtOAc/petroleum ether) to give the product.

**General procedure for synthesis of compound 7**: Diyne **5** (0.2 mmol), 3-hexyne (2 equiv), and Wilkinson's catalyst were stirred together in toluene (2 mL) at 90 °C under a nitrogen atmosphere. After the reaction was complete (by TLC), $Ag_2CO_3$ (1 equiv) and a second portion of $[RhCl(PPh_3)_3]$ (5 mol%) were added to the Schlenk tube under a nitrogen atmosphere, followed by 1,4-dioxane. Then, the mixture was stirred at 115 °C for about 4 h. After the reaction was complete (by TLC), the volatile compounds were removed in vacuo and the crude residue was purified by column chromatography on silica gel (EtOAc/petroleum ether) to give the product.

## Acknowledgements

We thank the National Science Foundation of China (21172239) for financial support.

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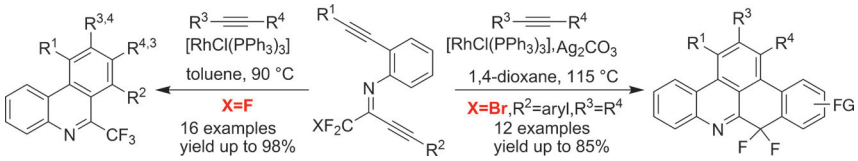
Received: January 25, 2013
Published online: ■■ ▮▮, 0000




**[2+2+2] Little boys**: Fluorine-containing multisubstituted phenanthridines have been synthesized through Rh-catalyzed alkyne [2+2+2] cycloaddition reactions (see scheme; FG = functional group). Polycyclic compounds were also obtained through Rh-catalyzed C–H difluoromethylenation.

**Cycloaddition Reactions**

*Y. Li, J. Zhu, L. Zhang, Y. Wu,* Y. Gong** ..... ▮▮▮▮–▮▮▮▮

**Synthesis of Fluorine-Containing Multisubstituted Phenanthridines by Rhodium-Catalyzed Alkyne [2+2+2] Cycloaddition and Tandem $sp^2$ C–H Difluoromethylenation**