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Copper-Catalyzed Site-Selective Direct Arylation of Triptycene

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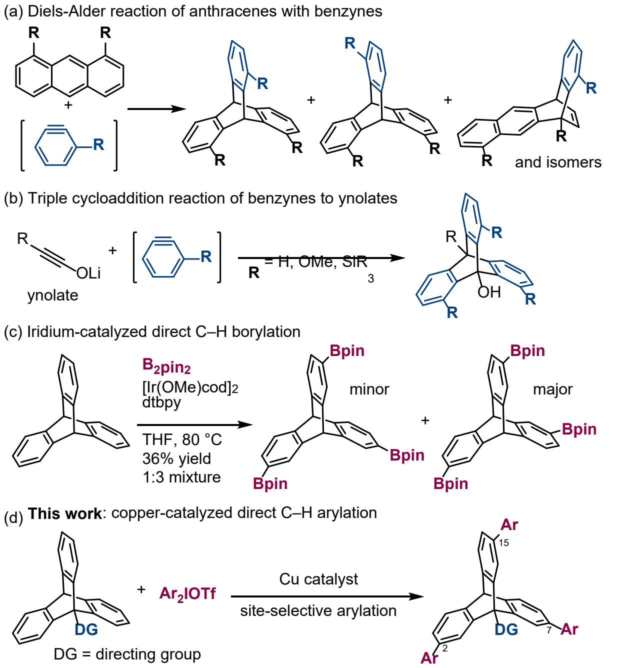
A site-selective direct C–H arylation protocol for triptycene skeleton is developed using copper catalyst and diaryliodonium reagents. With the aid of directing groups, C_3-symmetric trisubstituted triptycenes are selectively synthesized, and the structure was determined by the X-ray diffraction analysis. Further derivatization of the installed bromo functionalities are also described.

Keywords: Copper, C–H Activation, Triptycene

Triptycene is a paddle-wheel shaped aromatic hydrocarbon in which the three benzene rings are fused within a bicyclo[2.2.2]octatriene (barrelene) core.[1] Because of the unique three-dimensional rigid architecture, triptycene derivatives have found wide applications in many research fields involving supramolecular chemistry, molecular machine, host-gest chemistry, material science, etc.[2,3] Accordingly, there is a great demand for the development of efficient and controllable synthetic tools for manufacturing functionalized triptycenes.

A conventional synthetic method for the triptycene derivatives is the Diels-Alder reaction of anthracenes with benzynes (or quinones). It is hardly possible to control the regioselectivity of the cycloaddition event with any substituents on the periphery of the reactants, so that the target product needs to be separated from the complex mixture of isomers (Scheme 1a).[4] Moreover, the preparation of functionalized anthracenes suffers from cumbersome multi-step synthesis. As a potentially relevant transformation, Shindo *et al.* developed a sequential triple addition reaction of lithium ynolates to benzynes (Scheme 1b).[5] This excellent method offers an easy access to symmetrically-functionalized triptycenes with high regioselectivity, whereas the substitution pattern was rather limited. Electrophilic aromatic substitution[6,7] and iridium-catalyzed direct C–H borylation (Scheme 1c)[8] have also been adopted to functionalize the triptycene skeleton. The product distribution of these transformations is, however, totally governed by statistic factor, and the competing overreaction is usually inevitable.[9]

In order to address the synthetic limitation described above, we envisioned developing a site-selective direct functionalization protocol with the aid of transition-metal catalysis. Although the last few decades witnessed a tremendous achievement in the field of directing-group-assisted C–H activation chemistry,[10] there has been no report for the decoration of triptycene scaffolds upon this strategy. We assumed that the installation of appropriate functionality at the bridgehead position would facilitate the direct C–H transformation of the proximal three benzene rings. In this manuscript, we focused on a copper-catalyzed direct C–H arylation using diaryliodonium salts as arylating reagents due to the enhanced electrophilic nature of the Cu(III)-aryl species and the high regioselectivity (Scheme 1d).[11,12,13] This reaction system produces a series of 2,7,15-trisubstiuted C_3-symmetric triptycenes, which are difficult to be assembled through the conventional synthetic methods.


(a) Diels-Alder reaction of anthracenes with benzynes

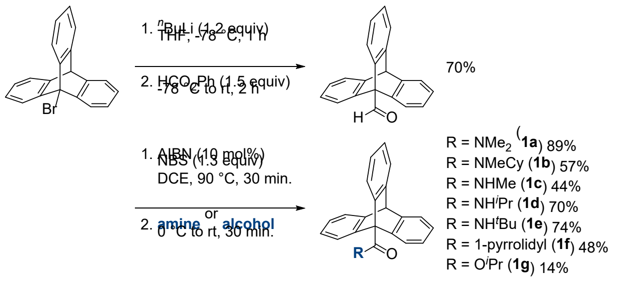
(b) Triple cycloaddition reaction of benzynes to ynolates

(c) Iridium-catalyzed direct C–H borylation

(d) **This work**: copper-catalyzed direct C–H arylation

Scheme 1. Representative Synthetic Methods for Functionalized Triptycenes.

At the outset of this study, we attempted to establish a synthetic method for introducing carbonyl-based directing groups at the bridgehead position (Scheme 2). A commerically available 9-bromotriptycene was treated with *n*-butyllithium, and the obtained lithium reagent was further reacted with phenylformate to give 9-formyltriptycene. This was converted to the corresponding acid bromide using NBS (*N*-bromosuccinimide) and a catalytic amount of AIBN (azodiisobutyronitrile).[14] Addition of any amine or alcohol produced the target amides **1a**–**1f** and ester **1g**. Direct transformation from the lithiated species to amides or esters using carbamoyl chlorides or chloroformate, respectively, was totally unsuccessful.



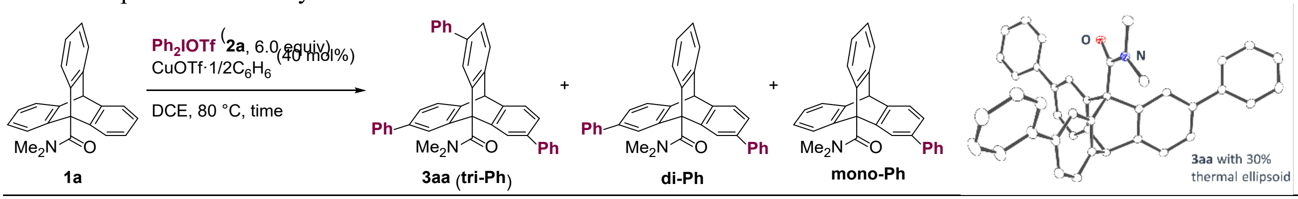
Scheme 2. Synthesis of 9-Substituted Triptycenes.

After the preliminary screening of the reaction conditions with these prepared substrates, the desired tri-arylated products were obtained using Ph$_2$IOTf as an arylating reagent in the presence of Cu complexes.[15] Consequently, optimization study was conducted using **1a** as a model substrate (Table 1). With 5.0 mol% of Cu(OTf)·1/2C$_6$H$_6$ catalyst and 4.0 equiv of Ph$_2$IOTf (**2a**), the target product **3aa** (tri-Ph) was obtained in 16% yield along with the di-Ph (52%) and the mono-Ph (29%) products (entry 1). The structure of **3aa** was unambiguously determined by the single crystal X-ray diffraction analysis.[16] Increased amount of the Cu catalyst (40 mol%) and **2a** (6.0 equiv) shifted the product distribution to the desired product up to 33% yield (entries 2 and 3), but further improvement was not achieved with the prolonged reaction time (entry 4). This was probably because decomposition of the hypervalent iodine reagent **2a** was competing under the conditions. To our delight, **3aa** was obtained in 48% yield when **2a** was added portionwise in four parts during the course of reaction (entry 5). In order to trap an excess acid byproduct (TfOH), we examined the effect of base additives. The addition of N^{i}Pr$_2$Et in a portionwise manner (added in three parts, immediately before the addition of **2a**) improved the yield of **3aa** to 57% (entry 6). Increased amount of the base did not significantly affected the yield (entries 7 and 8). With 1.0 equiv of N^{i}Pr$_2$Et in total, the amount of CuOTf·1/2C$_6$H$_6$ catalyst could be reduced to 10 mol% without significant drop of the productivity (entry 9). Other bases such as NEt$_3$ (entry 10) and DBU (entry 11) were not effective.

Since the increased loading of Cu catalyst (up to 150 mol%) did not improve the reactivity even when added portionwise, the moderate yield was not likely due to the catalyst deactivation but rather to the inhibition by side-products. Actually, a higher 73% yield of **3aa** was obtained in a two-pot procedure, where the crude mixture was again subjected to the same reaction conditions after aqueous work up (Scheme 3).

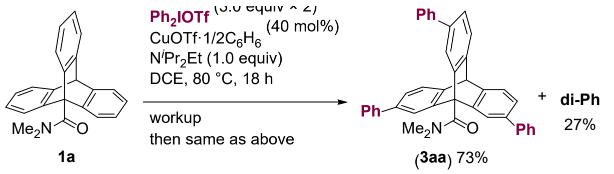
According to the literature,[17] we assume that the present reaction proceeds via a Heck-like mechanism (Scheme 4). CuOTf was oxidized by the iodonium reagent to generate Ph–Cu(OTf)$_2$ species. With the assistance of carbonyl coordination, the aryl group is transferred to the "meta" position of the triptycene core through a four-membered-ring transition state. Subsequent deprotonation furnishes the arylated product and CuOTf, closing the catalytic cycle.

Table 1. Optimization Study. [a)]

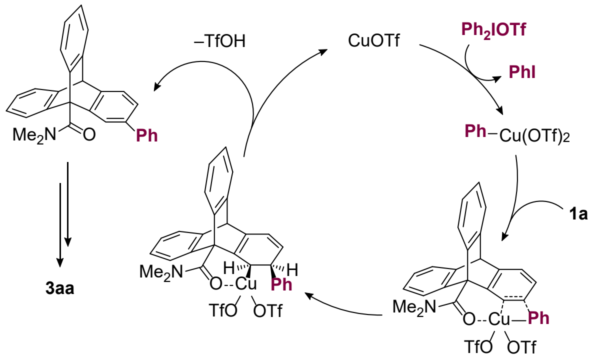


entry	deviation from the standard conditions	time	tri-Ph [b)]	di-Ph [b)]	mono-Ph [b)]
1	CuOTf·1/2C$_6$H$_6$ (5.0 mol%), **2a** (4.0 equiv)	16 h	16%	52%	29%
2	**2a** (4.0 equiv)	16 h	26%	54%	19%
3	--	40 h	33%	54%	13%
4	--	70 h	33%	53%	13%
5	**2a** (1.5 equiv × 4)	22 h	48%	47%	6%
6	**2a** (1.5 equiv × 4), N^{i}Pr$_2$Et (0.25 equiv × 3)	22 h	57%	41%	3%
7	**2a** (1.5 equiv × 4), N^{i}Pr$_2$Et (0.33 equiv × 3)	22 h	58% (42%)[c)]	40%	2%
8	**2a** (1.5 equiv × 4), N^{i}Pr$_2$Et (0.5 equiv × 3)	22 h	51%	45%	3%
9	CuOTf·1/2C$_6$H$_6$ (10 mol%) **2a** (1.5 equiv × 4), N^{i}Pr$_2$Et (0.33 equiv × 3)	22 h	53%	44%	3%
10	**2a** (1.5 equiv × 4), NEt$_3$ (0.5 equiv × 3)	22 h	45%	50%	5%
11	**2a** (1.5 equiv × 4), DBU (0.5 equiv × 3)	22 h	19%	57%	23%

[a)] Standard conditions: **1a** (0.05 mmol), **2a** (0.3 mmol), CuOTf·1/2C$_6$H$_6$ (0.02 mmol), DCE (2.0 mL).
[b)] The yield was determined by ^{1}H NMR analysis. [c)] Isolated yield.
Tf = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene



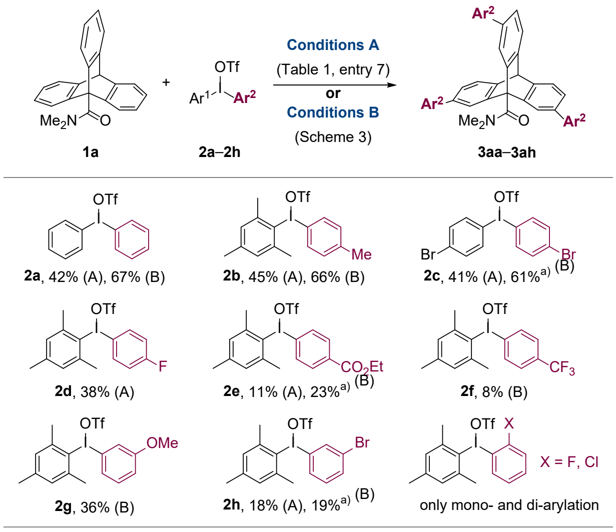
Scheme 3. Arylation of **1a** in a Two-pot Procedure. NMR yields are shown.



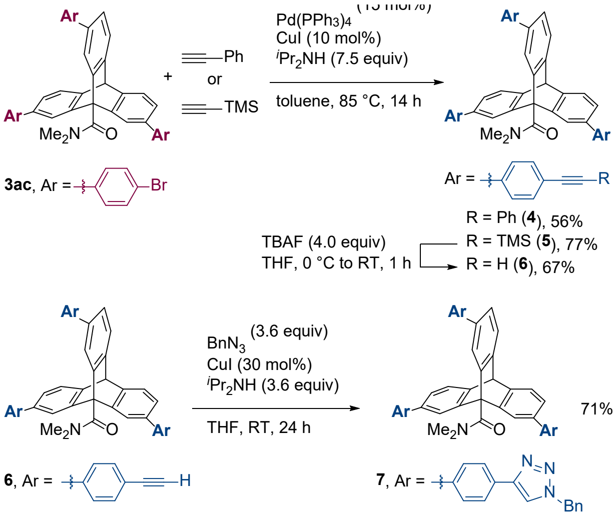
Scheme 4. Proposed Reaction Mechanism.

We next investigated the reaction efficiency of a series of substituted iodonium reagents under the reaction conditions of entry 7 in Table 1 (conditions A) and of Scheme 3 (conditions B). The values in Scheme 5 represents the yield of tri-arylated products. For the reaction with *para*-Me (**2b**), *para*-Br (**2c**), and *para*-F (**2d**) substituents, the corresponding products were isolated in 38~45% yields, being comparable to that of reaction with **2a**. Higher yields of **3aa** (67%), **3ab** (66%), and **3ac** (61%) were obtained with the conditions B. Electron-withdrawing ester (**2e**) and trifluoromethyl (**2f**) groups considerably retarded the reaction to give the products in lower yields. The meta-substituted aryl groups (**2g**, **2h**) also could be transferred selectively to the triptycene benzene rings. On the other hand, ortho-substituted iodonium reagents only afforded mono- and di-arylated products, and the formation of tri-arylated products was negligible.

The bromo (**3ac**, **3ah**) and ester (**3ae**) functionalities offer numerous possible transformations afterward, so that these compounds would be potentially useful C_3-symmetric triptycene building blocks. As a particular example for the derivatization of the product, we performed alkynylation of **3ac** (Scheme 6). The bromo groups were converted to the alkynyl groups under the standard Sonogashira coupling conditions to deliver **4** and **5** respectively in 56% and 77% yields. Deprotection of the TMS group on **5** was affected by TBAF (tetrabutylammonium fluoride) to afford the terminal alkyne **6**, which was further transformed into **7** via through the Huisgen cycloaddition reaction.



Scheme 5. Scope for the Arylating Reagents. Isolated yields for the tri-arylated products are shown. $^{a)}$ Determined by ^{1}H NMR analysis.



Scheme 6. Derivatization of the Products.

In summary, we have developed a copper-catalyzed site-selective arylation protocol with the aid of amide functionality placed at the bridgehead position. This report demonstrate the first example of directing-group-assisted C–H functionalization of the triptycene scaffold, producing C_3-symmetric tri-substituted triptycene derivatives exclusively. As exemplified in this study, the transition-metal-catalyzed direct C–H activation methodology would be a proper mean of decollating the triptycene periphery.

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The authors declare no competing financial interest.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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