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RESEARCH ARTICLE

Palladium-Catalyzed α-Selective Halogenation of Triptycene Using Sulfur Directing Group

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Dedication ((optional))

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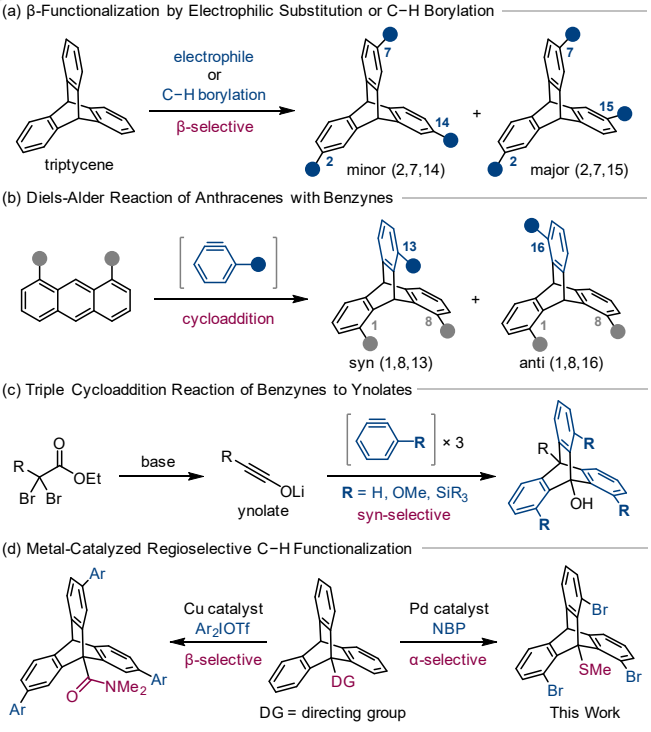
Abstract: Functionalized triptycene derivatives have attracted significant research interest because of their potential applications in many research fields. Although the conventional Diels-Alder reaction of anthracenes with benzynes has been a versatile synthetic tool for functionalized triptycenes, it is hardly possible to control the product regioselectivity. In this report, we demonstrate the selective synthesis of 1,8,13-trisubstituted triptycenes by Pd-catalyzed α-bromination. As for the directing group, SMe group was the most effective to facilitate the halogenation of the proximal three benzene rings. The obtained product was further derivatized through allylation and Rh-catalyzed hydroboration reactions.

Introduction

Triptycene is an aromatic hydrocarbon with a unique paddle-wheel configuration where three benzene rings are combined within the barrelene core structure. Since the first synthesis of this molecule by Bartlett in 1942,[1] functionalized triptycenes as well as related iptycene derivatives have attracted considerable interest because of their characteristic three-dimensional rigid architecture. Application of these compounds covers many research fields such as material science, host-gest chemistry, molecular machine, etc.[2] Accordingly, a significant interest has focused on achieving effective and controllable synthesis for functionalized triptycene derivatives.

Direct functionalization of the triptycene skeleton by electrophilic aromatic substitution preferentially proceeds at β-positions,[3] and the product ratio would be statistically governed (Scheme 1a).[4] An Ir-catalyzed C–H borylation has also been utilized for directly installing functional groups to the triptycene core, and the selectivity in this method can be treated similarly to that of the electrophilic substitution.[5] Therefore, the conventional Diels-Alder reaction of anthracenes with benzynes has been only the synthetic method to obtain α-functionalized triptycene derivatives (Scheme 1b). As demonstrated in early reports by Kadosaka[6] and Averill,[7] this approach produces both syn/anti isomers, and it is hardly possible to control the regioselectivity of the cycloaddition event. Moreover, multi-step synthesis is usually inevitable for the preparation of 1,8-disubstituted anthanthrenes and functionalized benzyne precursors. It is thus highly challenging to systematically construct the C_3-symmetric compounds.



Scheme 1. Synthesis of functionalized triptycene derivatives.

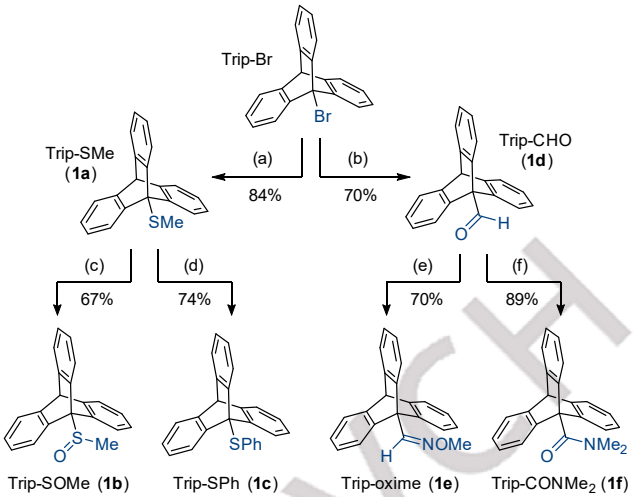
In 2017, Sindo achieved regioselective synthesis of 1,8,13-trisubstituted triptycenes based on the unprecedented triple cycloaddition reaction of ynolates (Scheme 1c).[8] Afterword, this concept was successfully applied to the synthesis of 1,8,13-trisilyltriptycenes.[8b] It is notable that triptycene derivatives with this substitution pattern have widely been investigated as functional molecules owing to their Janus-type rigid structures.[9,10]

Our group has recently focused on the transition-metal-catalyzed direct C–H functionalization[11] of the triptycene skeleton, and developed a Cu-catalyzed regioselective arylation with the aid of an amide directing group placed at the bridgehead C9 position (Scheme 1d).[12] This reaction system was effective for synthesizing 2,7,14-trisubstiuted triptycenes, whereas directing-group-assisted α-selective functionalization has not been developed to date. Herein, we report a Pd-catalyzed α-selective bromination of triptycene.[13,14] Among the tested directing groups, an SMe group was the most effective to facilitate the halogenation of the proximal three benzene rings. The obtained product would be a useful building block for 1,8,13-trisubstituted triptycene derivatives because the halogen functionalities offer possible transformation modes afterward.

Results and Discussion

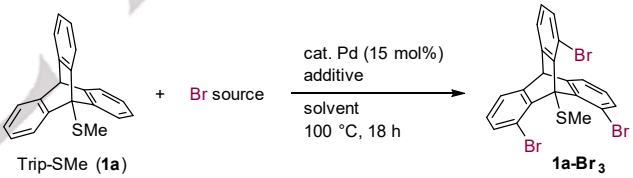
At the outset, we prepared a series of 9-functionalized triptycene derivatives from a commerically available Trip-Br (Trip = 9-triptycenyl) to find an effective directing group for the target reaction (Scheme 2, see the SI for details). Lithiation and trapping with disulfide afforded Trip-SMe (**1a**) in 84% yield, and the corresponding sulfoxide (**1b**) was obtained by oxidation with *m*CPBA. Since trapping of the lithium reagent with diphenyl disulfide was unsuccessful, Trip-SPh (**1c**) was synthesized according to the report by Sanford using diphenyliodonium triflate.[15] Trip-CHO (**1d**) was prepared according to the literature procedure adopting phenylformate as the carbonyl source.[11] The corresponding oxime (**1e**) and amide (**1f**) were readily obtained by condensation with methylhydroxylamine and amidation through the acid bromide, respectively.

We then optimized reaction conditions for the direct halogenation adopting Trip-SMe (**1a**) as a model substrate (Table 1, see the SI for additional data). Upon treatment with NBS (*N*-bromosuccinimide) in the presence of $Pd(OAc)_2$ catalyst (15 mol%), the target 1,8,13-trihalogenated product **1a-Br$_3$** was obtained in 16% yield (entry 1). We tested several palladium catalysts, but these were not effective for the present reaction (entries 2-4). As regards halogenating reagents, NBP (*N*-bromophthalimide) achieved better productivity than DBDMH (1,3-Dibromo-5,5-dimethylhydantoin) to give **1a-Br$_3$** in 43% yield (entries 5,6). Some additives were then examined to improve reaction efficiency (entries 7-12), and higher yields were obtained when 20 mol% of $PhCO_2H$ (entry 9) or PivOH (entry 10) was used. It is notable that CsOPiv did not affect the productivity (entry 11), whereas a strong hydrogen bonding donor HFIP (hexafluoro-2-propanol) significantly retarded the reaction (entry 12). After screening solvents, TCE (1,1,2,2-tetrachloroethane) afforded the highest 85% yield (entry 13). This reaction could be conducted at 0.5 mmol scale to give **1a-Br$_3$** in 72% yield (entry 14).



Scheme 2. Synthesis of 9-substituted triptycene derivatives: (a) *n*-BuLi (1.2 eq) in THF at −78°C, then dimethyldisulfide (1.2 eq); (b) *n*-BuLi (1.2 eq) in THF at −78°C, then HCO_2Ph (1.5 eq); (c) *m*CPBA (1.5 eq) in DCE at 0 °C; (d) Ph_2IOTf (1.5 eq), $Cu(OTf)_2$ (5.0 mol%) in DCE at 100 °C; (e) $MeONH_2$·HCl (1.5 eq), NaOAc (2.0 eq) in EtOH at 90 °C; (f) NBS (1.3 eq), AIBN (10 mol%) in DCE at 90 °C, then Me_2NH (2.3 eq) at 0 °C.

Table 1. Optimization of reaction conditions. [a]

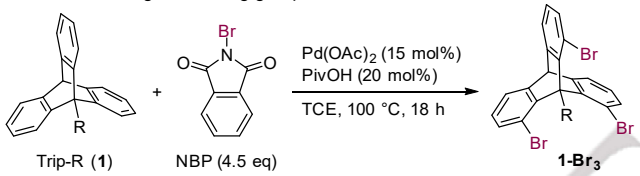


entry	catalyst	Br source	solvent	additive	yield [b]
1	$Pd(OAc)_2$	NBS	DCE	--	16%
2	$PdCl_2$	NBS	DCE	--	trace
3	$Pd(TFA)_2$	NBS	DCE	--	n.d.
4	$Pd(OPiv)_2$	NBS	DCE	--	n.d.
5	$Pd(OAc)_2$	NBP	DCE	--	43%
6	$Pd(OAc)_2$	DBDMH	DCE	--	7%
7	$Pd(OAc)_2$	NBP	DCE	K_2CO_3	n.d.
8	$Pd(OAc)_2$	NBP	DCE	AcOH	26%
9	$Pd(OAc)_2$	NBP	DCE	$PhCO_2H$	54%
10	$Pd(OAc)_2$	NBP	DCE	PivOH	64%
11	$Pd(OAc)_2$	NBP	DCE	CsOPiv	45%
12	$Pd(OAc)_2$	NBP	DCE	HFIP [c]	5%
13	$Pd(OAc)_2$	NBP	TCE	PivOH	85%
14	$Pd(OAc)_2$	NBP	TCE	PivOH	72% [d]

[a] Reaction conditions: **1a** (0.1 mmol), Pd catalyst (15 mol%), Br source (0.45 mmol as Br atom), and additive (20 mol%) in solvent (2.0 mL) were heated at 100 °C for 18 h. [b] Estimated by ^{1}H NMR. [c] 0.2 mL of HFIP (hexafluoro-2-propanol) was used. [d] 0.5 mmol scale. DCE = 1,2-dichloroethane, TCE = 1,1,2,2-tetrachloroethane, n.d. = not detected.

With the optimal reaction conditions in hand, we examined the effect of directing groups (Table 2).[16] As mentioned above, Trip-SMe (**1a**) was successfully converted to the desired halogenation product, and it could be isolated in 67% yield (entry 1). In sharp contrast, Trip-SOMe (**1b**) and Trip-SPh (**1c**) were considerably less reactive to only produce mono-bromination products in small quantities (entries 2,3). Aldehyde (**1d**), oxime (**1e**), and amide (**1f**) directing groups were also not effective for this transformation, and these reaction ended up with complex mixtures (entries 4-6). We assume that the SMe directing group was particularly effective for the present reaction because of its small size. The bridgehead position of the triptycene scaffold is relatively congested, and would get more sterically hindered after the bromination. Sterically more demanding substituents (**1b**–**1f**) would encumber the C9–DG bond rotation and thereby could not be suitable directing groups.

Table 2. Screening of directing groups. [a]



entry	Trip-R	yield [b]	Note [b]
1	**1a**	85%	67% isolated yield
2	**1b**	n.d.	75% **1b** recovered, mono-Br detected
3	**1c**	n.d.	52% **1c** recovered, mono-Br detected
4	**1d**	n.d.	**1d** not recovered, complex mixture
5	**1e**	n.d.	51% **1e** recovered, complex mixture
6	**1f**	n.d.	34% **1f** recovered, complex mixture

[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (15 mol%), NBP (0.45 mmol), and PivOH (20 mol%) in TCE (2.0 mL) were heated at 100 °C for 18 h. [b] Estimated by ^{1}H NMR and GC-MS analyses. TCE = 1,1,2,2-tetrachloroethane, n.d. = not detected.

The structure of **1a-Br$_3$** was unambiguously confirmed by single crystal X-ray analysis.[17] As expected, the Br substituents were installed at the *ortho* positions with respect to the directing group (Figure 1). This outcome would invalidate electrophilic substitution mechanism. The triptycene framework was slightly distorted due to the steric repulsion, and two benzene rings close to the SMe group and the other one opposite to the SMe group were inequivalent in NMR spectra.

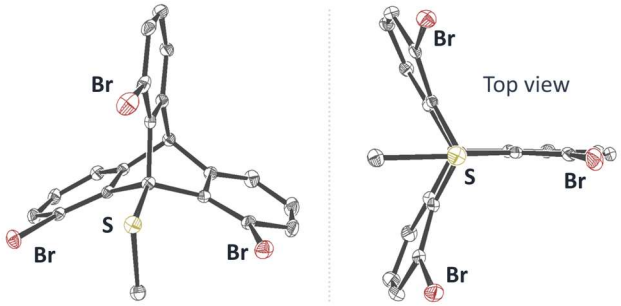
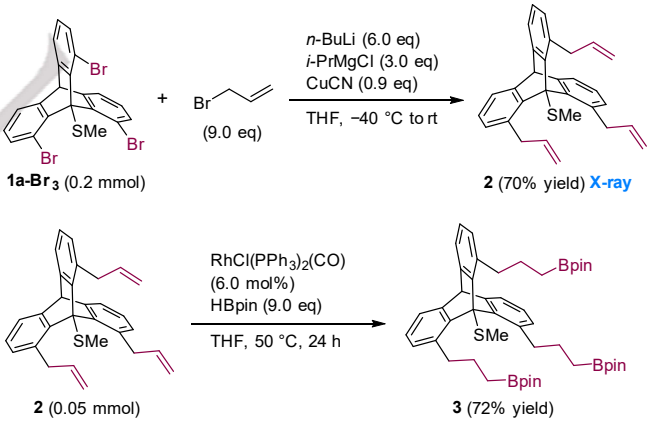


Figure 1. ORTEP drawings of **1a-Br$_3$** with 40% thermal ellipsoid. Hydrogen atoms are omitted for clarity. Single crystals were obtained by *n*-pentane vapor diffusion into the $CHCl_3$ solution.

Next, we examined derivatization of the halogenated product to showcase its synthetic utility (Scheme 3). **1a-Br$_3$** was first treated with *n*-BuLi and *i*-PrMgCl to prepare the corresponding nucleophilic aryl-metal species. This was successively reacted with allyl bromide to give the desired product **2** in 70% yield, and its structure was confirmed by the X-ray crystallography.[17] This compound would be a versatile building block for 1,8,13-trisubstituted triptycene derivatives because the terminal alkene groups offer various possible functionalizations afterward. As a representative example, we examined hydroboration using pinacol borane (HBpin) in the presence of $RhCl(PPh_3)_2(CO)$ catalyst. To our delight, the target product **3** was obtained in 72% yield.



Scheme 3. Derivatization of the halogenated triptycene.

Conclusion

In this work, we have achieved a Pd-catalyzed site-selective halogenation of triptycene scaffold adopting an SMe directing group. Under the optimized conditions, 1,8,13-tribromotriptycene **1a-Br$_3$** was obtained in high yield, whereas other carbonyl-based directing groups were totally ineffective for the present reaction. As demonstrated in the derivatization of **1a-Br$_3$**, the developed reaction would be an effective method for synthesizing various 1,8,13-trisubstituted triptycene derivatives, which have not been readily accessible by traditional synthetic methods.

Experimental Section

Pd-catalyzed bromination of Trip-SMe (**1a**): In a two-neck round-bottom flask equipped with an N_2 balloon and a rubber septum, Trip-SMe (30 mg, 0.1 mmol), PivOH (2.0 mg, 20 mol%), $Pd(OAc)_2$ (3.4 mg, 15 mol%), and NBP (102 mg, 0.45 mmol) were dissolved in TCE (2.0 mL). The mixture was heated at 100 °C for 18 h. The resulting suspension was diluted with H_2O, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by silica gel chromatography (hexane/EtOAc = 10/1) and GPC ($CHCl_3$) to give **1a-Br$_3$** as white solid in 67% yield (36 mg).

1,8,13-tribromo-9-methylthiotriptycene (**1a-Br$_3$**): m.p. >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.45 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.37 (dd, *J* = 7.1, 1.4 Hz, 2H), 7.24 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.18 (dd, *J* = 7.2, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.1, 7.1 Hz, 2H), 6.77 (dd, *J* = 8.0, 7.2 Hz, 1H), 5.15 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 150.7, 147.6, 140.8, 140.1, 135.1, 133.5, 128.0, 126.9, 123.4, 123.0, 121.2, 117.5, 57.2, 20.3; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{14}{}^{79}Br_2{}^{81}BrS$ 536,8340; Found 536.8369.

Supporting Information

The authors have cited additional references within the Supporting Information.[17-19]

Acknowledgements

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Keywords: Halogenation • Palladium • C-H activation • Triptycene

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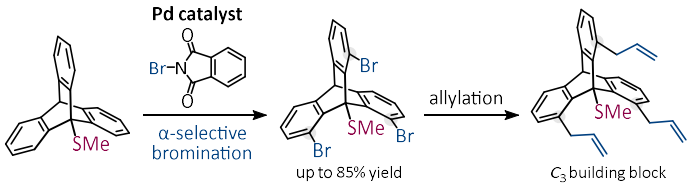

Functionalized triptycene derivatives have attracted significant research interest because of their potential applications in many research fields. In this report, we demonstrate the synthesis of 1,8,13-trisubstituted triptycenes via palladium-catalyzed α-selective bromination. The sulfide directing group was effective to facilitate the halogenation of the proximal three benzene rings.

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