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Construction of Partially Protected Nonsymmetrical Biaryldiols via Semipinacol Rearrangement of *o*-NQM Derived from Enynones

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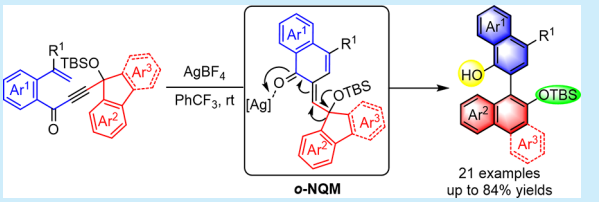
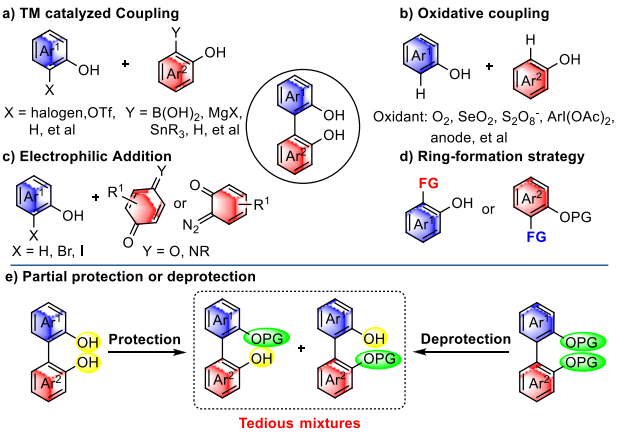
ABSTRACT: The construction of partially protected nonsymmetrical biaryldiols catalyzed by $AgBF_4$ has been achieved. The approach facilitates the formation of two new aryl rings and the introduction of two hydroxyl groups (one free and one TBS-protected) via the *o*-NQM generation/semipinacol rearrangement cascade, featuring high atom- and step-economy to afford a diverse array of partially protected nonsymmetrical biaryldiols under mild conditions.



Nonsymmetrical biaryldiol motifs are prevalent in a wide range of natural products, pharmaceuticals, ligands, and synthetic building blocks.[1] Traditionally, protocols for the synthesis of nonsymmetrical biaryldiols mainly rely on the formation of $C(sp^2)-C(sp^2)$ bonds, including transition-metal-catalyzed cross coupling and oxidative cross-coupling process.

Following the transition-metal-catalyzed cross-coupling strategy[2] (Scheme 1a), the substrates are activated by the introduction of specific leaving groups or directing groups. These burdensome steps impinge on both the atom-, step-economy and cost of noble metal complexes. In contrast, the oxidative coupling reactions[3] (Scheme 1b) offer a superior alternative for a sustainable process. However, in such reactions, both coupling partners are typically limited to phenols with electron-donating substituents. In the context of nonsymmetrical diaryldiols, the selectivity of the cross coupling is hampered by insufficient differences in redox potentials between two coupling partners.[3,4] The indirect oxidative cross coupling (Scheme 1c) can be achieved by prior oxidation of one coupling partner, which is separated in time and space to be assembled with another nucleophilic partner.[5] Besides the formation of $C(sp^2)-C(sp^2)$ bonds, the biaryls also can be accessed from an aryl substituent upon construction of a new arene ring[6] (Scheme 1d).

Scheme 1. Construction of Nonsymmetrical Biaryldiols and Their Protection



Furthermore, enhanced chemo- and regioselective transformation of unsymmetrical biaryldiols is a crucial and challenging task that requires selective protection of two hydroxy groups.[1e,f] The blocking of one hydroxyl with easily removable protecting groups in a symmetrical biaryldiol is achieved by applying minimum amounts of protecting reagent or by partial deprotection of completely protected biaryldiols.[7] However, this strategy often leads to complex product mixtures, requiring tedious workup and resulting low yield when it was extended to nonsymmetrical biaryldiols as the two hydroxyl groups react similarly[7] (Scheme 1e). One of the most general methods to access partially protected nonsymmetrical biaryldiols is the late-state functionalization from symmetrical precursors[8] (Scheme 2a). The direct cross-coupling to access partially protected biaryldiols via electroorganic synthesis was recently realized by Waldvogel and co-workers[9] (Scheme 2b).

In connection with our interest in the generation and application of quinone methide intermediates via ring-formation strategy[10] and also inspired by the reaction aptitude of the semipinacol rearrangement,[11] we envisioned that an *o*-naphthoquinone methide (*o*-NQM) generation/semipinacol

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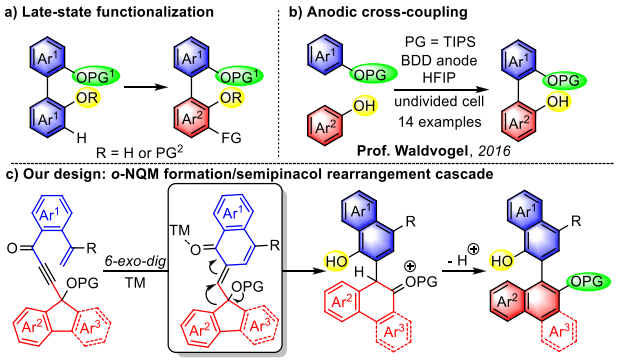
Scheme 2. Construction of Partially Protected Nonsymmetrical Biaryldiols

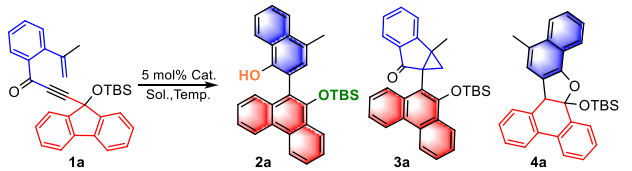


rearrangement cascade of enynone with a properly installed protected 9-fluorenol moiety may be viable to afford partially protected nonsymmetrical biaryldiols (Scheme 2c). This reaction allows the formation of two new aryl rings and the introduction of two hydroxyl groups (one free and one protected) by using readily available enynones as starting materials in one step, featuring high efficiency and atom-economy.

With these considerations, we first tested the feasibility of the designed cascade process using enynone **1a** bearing a TBS-protected 9-fluorenol moiety as model substrate. As shown in Table 1, cationic Au(I) was initially utilized as catalyst owing to its high efficiency in promoting the alkyne cyclization. To our delight, the desired partially protected nonsymmetrical biaryldiol product **2a** was detected in 20% yield. However, the majority of the starting material was converted into the cyclopropane product **3a** (78%, entry 1). Encouraged by this observation, several catalysts, which were proven efficient to induce the generation of *o*-NQM,[10a10b] were examined. When $Zn(OTf)_2$ and $Cu(OTf)_2$ were applied as catalysts, the full conversion of **1a** was achieved, furnishing the desired product **2a** in 42% and 53% yield, respectively (entries 2 and 3). The yield of product **2a** increased to 55% by using $AgBF_4$ as the catalyst (entry 4), accompanied by 26% byproduct **4a**, which was attributed to the intramolecular nucleophilic attack of the silyl protected onium.[12] Solvents were evaluated as well to promote the selectivity of **2a** and **4a** (entries 4−7). The highest yield was obtained with $PhCF_3$ as solvent, affording **2a** in 74% yield. Further investigation of other silver salts finally identified $AgBF_4$ as the optimal catalyst (entries 7−10).

On the basis of the optimized reaction condition (Table 1, entry 7), the substrate scope was then examined. As shown in Scheme 3, a broad range of enynones **1** could behave as suitable *o*-NQM precursors. For example, in addition of substrate **1a**, enynones with different substituents at the tethered Ar^1 rings were well tolerated, affording the nonsymmetrical silyl protected diaryldiols **2a−h** in moderate to good yields (54−82%). The inferior effect of the electron-donating group at Ar^1 was observed, producing the desired products **2c** (54%) and **2f** (58%) in diminished yields. It is worth mentioning that this reaction was also applicable to thienylene-, benzofuran-, and naphthalene-fused enynones, giving the corresponding products **2i−k** in 34−70% yields. For

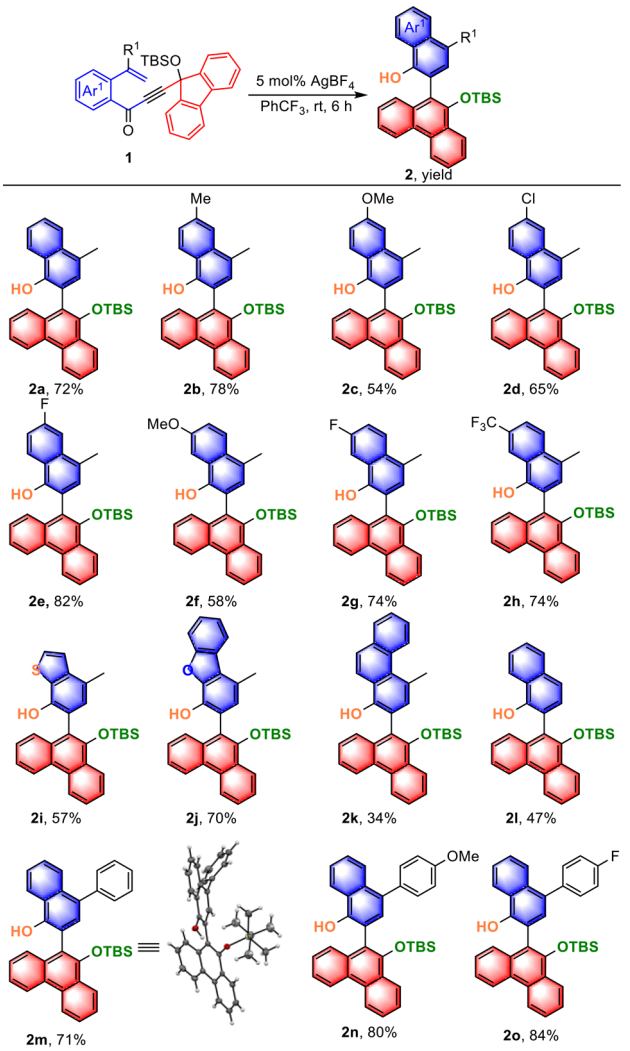
Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (mol %)	sol	temp (°C)	**2a**(%)	**3a**(%)	**4a**(%)
1	$IPrAuBF_4$ (5)	DCE	25	20	78	
2	$Zn(OTf)_2$ (10)	DCE	80	42		
3	$Cu(OTf)_2$ (10)	DCE	25	53		
4	$AgBF_4$ (5)	DCE	25	55		26
5	$AgBF_4$ (5)	DCM	25	40		25
6	$AgBF_4$ (5)	$PhCH_3$	25	33		
7	**$AgBF_4$(5)**	**$PhCF_3$**	**25**	**74**		**9**
8	AgOTf (5)	$PhCF_3$	25	58		14
9	$AgSbF_6$ (5)	$PhCF_3$	25	46		23
10	$AgNTf_2$ (5)	$PhCF_3$	25	58		8

[a]The reaction was performed under N_2 and anhydrous solvents; **1a** (0.1 mmol) in 1 mL solvent. The yield was determined by ^1H NMR spectroscopy with dimethyl terephthalate as internal standard.

Scheme 3. Substrate Scope of the Enynone[a]



[a]Reaction conditions: 5 mol % of $AgBF_4$, **1** (0.2 mmol), 2 mL $PhCF_3$; isolated yield.

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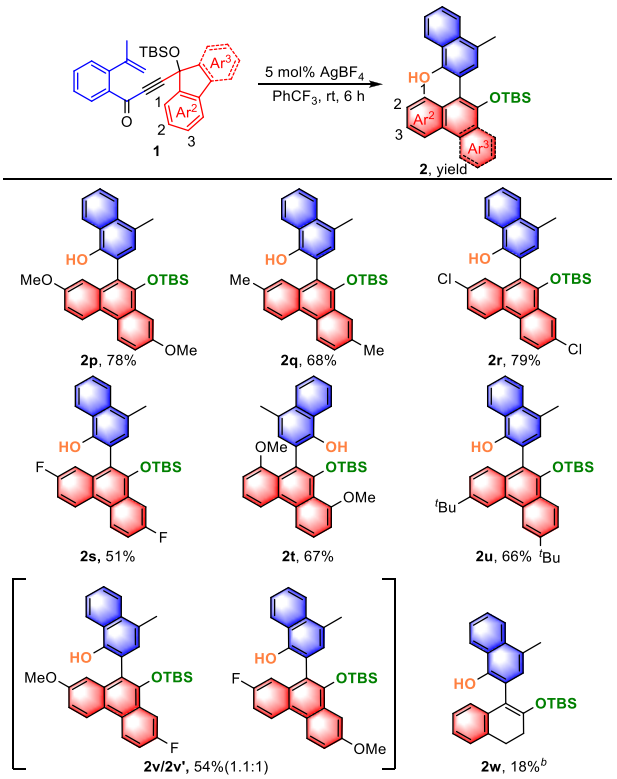
the enynone with a simple vinyl group, the desired product **2l** was obtained in 47% yield. The inferior performance of substrates **1k** and **1l** was attributed to the formation of cyclopropane byproducts.[13] The enynones with an aryl group of R^1 at the internal olefinic carbon were suitable substrates, affording the corresponding products **2m−o** in good yields (71−84%). The structure of the desired products was confirmed by single-crystal X-ray diffraction analysis of product **2m**.

In order to increase the generality of this reaction, we next considered extending the substituted fluorene moiety (Scheme 4). The formation of desired products showed that the

Scheme 4. Substrate Scope of Fluorene Moiety[a]

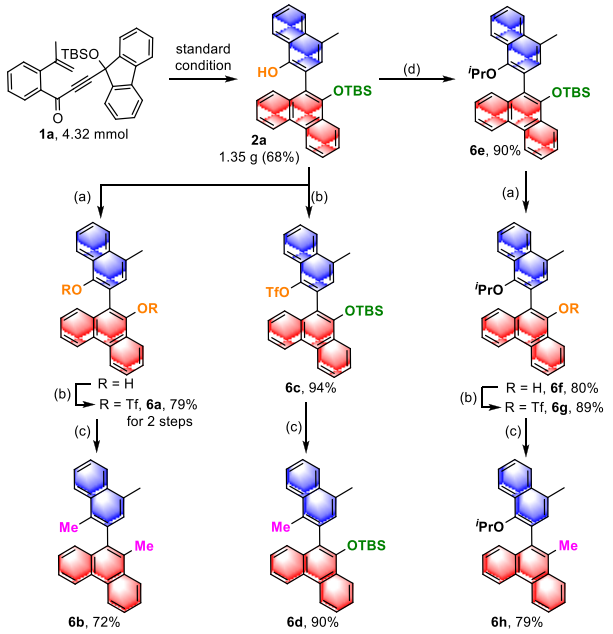


[a]Reaction conditions: 5 mol % of $AgBF_4$, **1** (0.2 mmol), 2 mL of $PhCF_3$; isolated yield. [b]The reaction was carried out at 60 °C.

substituents with different electron properties at 2-position of the fluorene were well tolerated, providing the desired products **2p−s** in 51−79% yields. It was found that the fluorenes with electron-deficient groups produced inferior yields (**2s**, 51%) compared to electron-rich or neutral ones (**2p−r**, 68−79%), which is in accordance with the feature of semipinacol rearrangement. When the enynones derived from 1,1′- or 3,3′-disubstituted fluorenone were used, 1,1′-MeO- or 3,3′-^{t}Bu-disubstituted products were obtained in good yield (**2t**, 67% and **2u**, 66%). In addition to symmetrical fluorene moieties, unsymmetrical fluorene bearing substituents with different electron properties were also examined. However, there is no obvious migration selectivity between MeO- and F-substituted phenyl groups (**2v**/**2v′** = 1.1:1). Higher temperature (60 °C) was required for the conversion of substrate **1w** (derived from indanone) to afford the aryl migration product **2w** in a diminished yield (18%).

To demonstrate the synthetic flexibility of this protocol, the derivatization of partially protected nonsymmetrical biaryldiol **2a** was further elaborated (Scheme 5). First, synthesis of

Scheme 5. Derivatization of Product 2a[a]



[a]TBAF, THF, 0 °C; [b]Tf_2O, pyridine, DCM, 0 °C; [c]MeMgBr, $Ni(dppp)Cl_2$, THF, 80 °C; [d]^{i}PrOH, DIAD, PPh_3, THF, −78 °C to rt.

product **2a** was easily scaled up to gram scale without loss of yield (68%, 1.35 g). The deprotection of the TBS and conversion to biaryl triflate **6a** allowed the modification of two hydroxyl groups at the same time (**6b**). The direct triflation of **2a** following Kumada coupling afforded the single modification product **6d**, keeping the TBS-protected hydroxyl untouched. Finally, the further protection of free hydroxy in **2a** by Mitsunobu reaction with ^{i}PrOH and conversion to triflate **6g** allowed the modification of the opposite hydroxyl position (**6h**).

To elucidate the reaction mechanism, several control reactions were then conducted (Scheme 6a). It was noticed that the cyclopropane byproducts were observed in some cases (**3a**, **3k**, and **3l**). But the possibility of the rearrangement of the cyclopropane moiety to access the naphthalene ring[14] was excluded by subjecting the cyclopropane **3a** to the standard reaction conditions, in which no conversion was observed. Although the *o*-NQM intermediate was usually too reactive to be isolated, the steric bulk TBS-protected fluorene moiety herein could help to enhance the stability.[15] For example, the key intermediate *o*-NQM **5a** could be successfully isolated in 79% yield when THF was used as the solvent. The *o*-NQM **5a** can be converted into the desired product **2a** under the standard conditions in 76% yield. With the evidence of the formation of the *o*-NQM, a plausible mechanism was then proposed as Scheme 6b. Initial silver-catalyzed 6-*exo*-*dig* cyclization of enynone **1** induced the generation of *o*-NQM,[10a10b] followed by a semipinacol rearrangement under the activation of catalyst to give the desired product **2** (path A). The cyclopropane byproducts should come from the tandem reaction of cycloisomerization of 1,6-enyne[16] and 1,2-aryl migration of the metal carbenoid intermediate (path B).

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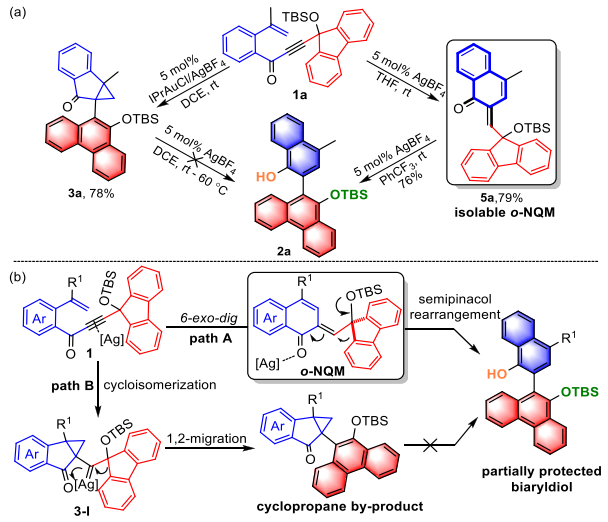
Scheme 6. Control Experiment and Plausible Reaction Mechanism



In summary, we have established an efficient approach for the construction of nonsymmetrical partially silyl-protected 2,2′-biaryldiols through the *o*-NQM generation/semipinacol cascade. This transformation features high atom- and step-economy, providing a broad range of partially protected 2,2′-biaryldiols allowing further flexible modifications. Investigation on the asymmetric version to access axially chiral biaryldiols is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03717.

Experimental procedures, characterization data, and copies of NMR spectra for substrates and products (PDF)

Accession Codes

CCDC 2015562 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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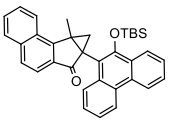
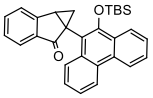
(13) Formation of cyclopropane products (the *dr* ratio was attributed to the rotation of the axis):



3k, 60% (*dr* = 1.1:1)



3l, 49% (*dr* = 1:1)

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