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EDGE ARTICLE

Lipshutz-type Bis(amido)argentates for Directed *ortho* Argentation†

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Bis(amido)argentate $(TMP)_2Ag(CN)Li_2$ (**3**, TMP-Ag-ate; TMP = 2,2,6,6-tetramethylpiperidido) was designed as a tool for chemoselective aromatic functionalization *via* unprecedented directed *ortho* argentation (DoAg). X-Ray crystallographic analysis showed that **3** takes a structure analogous to that of the corresponding Lipshutz cuprate. DoAg with this TMP-Ag-ate afforded multifunctional aromatics in high yields in processes that exhibited high chemoselectivity and compatibility with a wide range of functional groups. These included organometallics- and transition metal-susceptible substituents such as methyl ester, aldehyde, vinyl, iodo, (trifluoromethanesulfonyl)oxy and nitro groups. The arylargentates displayed good reactivity with various electrophiles. Chalcogen (S, Se, and Te) installation and azo coupling reactions also proceeded efficiently.

Introduction

Copper and silver are categorized as congeneric elements, being vertically adjacent in the periodic table. They have many similarities, including electronegativity (Cu 1.9 vs Ag 1.9)[1] and coordination geometry. However, whereas organocopper species have opened up many new avenues in organic synthesis,[2] the silver analogues are quite poorly characterized,[3] partly due to a lack of efficient preparative methods (Fig. 1a). For example, organocopper (R–Cu(I)) compounds are commonly prepared by the oxidative cupration of organic halides with Cu(0).[4] Unfortunately, this method cannot be applied to the preparation of organosilver (R–Ag(I)) compounds, because the Ag(0→I) redox potential is 0.8 V (Fig. 1b).[5,6] Neither hydro (or carbo)-metalation nor halogen-metal exchange, which are also effective methods for the preparation of organocopper compounds, have been effectively applied to organosilver chemistry to date.[7] Transmetalation from organometallics to an Ag(I) source is another route offering potential access to the corresponding organosilver species.[7b-c,8] However, the high reactivity (including wrt silver salts) of commonly used organolithiums and organomagnesiums severely restricts the employment of functionalized aromatic compounds as substrates. Directed *ortho* metalation (DoM) is another synthetic option for the regioselective preparation of aryl metal compounds[9,10] and could offer a route to aromatic silver complexes of a type that have recently received attention as potential reaction intermediates.[8l-n] Here we present an unprecedented directed *ortho* argentation (DoAg) reaction using a newly designed silver ate base, and demonstrate its applicability to the derivatization of a range of functionalized aromatics.

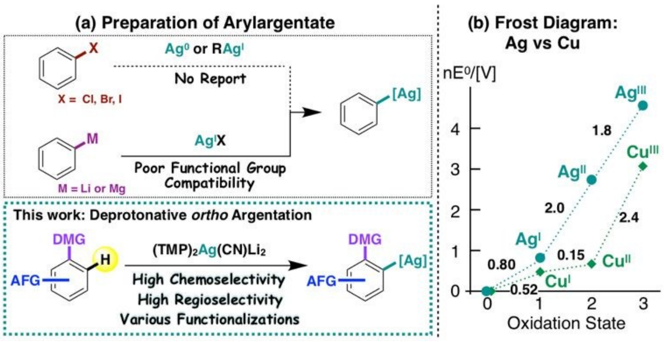

Fig. 1 Preparative Strategies of Arylargentate, and Comparison of Electrochemical Properties of Copper and Silver.

Results and discussion

We initially screened Ag-ate bases prepared by combining a range of silver salts and amido ligands for DoAg using *N*,*N*-diisopropylbenzamide (**1a**) as a model substrate, followed by trapping with iodine (Table 1). The use of silver(I) salts with equimolar TMPLi failed to provide the corresponding iodinated product **2a** (Entries 1 and 2). We next assessed the reactivity of TMP-argentates prepared from several silver sources using a

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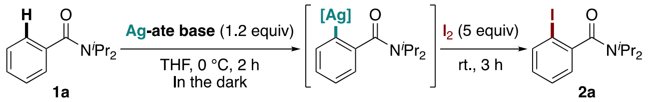
two-fold excess of TMPLi (Entries 3-6). $(TMP)_2Ag(CN)Li_2$ **3**, generated from silver cyanide, uniquely gave the desired product **2a**,[11] whereas other TMP-argentates were totally unproductive (Entry 6 vs. Entries 3-5). Moreover, **3** was capable of deprotonating two equivalents of substrate **1a** (Entry 7). From the viewpoint of practical use, it is important to emphasize that AgCN is comparable to CuCN in price.[12] Next, we examined amido ligands and solvents. The HMDS-argentate failed to give **2a**, presumably due to its low basicity (Entry 8). Meanwhile, in contrast to the poor yield obtained with $(^iPr_2N)_2Ag(CN)Li_2$,[13] **2a** was obtained quantitatively by using $(Cy_2N)_2Ag(CN)Li_2$ (Entries 9 vs. 10). This result is practically of great importance in terms of cost reduction.[14] The heteroleptic amidoargentate Me(TMP)Ag(CN)Li_2 proved unproductive (Entry 11).[15] Lastly, THF was found to be a particularly effective solvent for *Do*Ag (Entry 6 vs. Entries 12-15).[16] It is worth noting that neither **3** nor the putative intermediate arylargentate generated was sensitive to light, meaning that all *Do*Ag operations can be conducted without shading tools (Entry 16). Based on these data, all subsequent experiments were conducted without special precautions to exclude light.

Table 1 Optimization of Conditions



Entry	Ag-ate base	Solvent	Yield (%)	Entry	Ag-ate base	Solvent	Yield (%)
1	$(TMP)Ag(NO_3)Li$	THF	ND	9	$(^iPr_2N)_2Ag(CN)Li$	THF	11
2	(TMP)Ag(CN)Li	THF	ND	10	$(Cy_2N)_2Ag(CN)Li_2$	THF	99
3	$(TMP)_2Ag(NO_3)Li_2$	THF	ND	11	$Me(TMP)Ag(CN)Li_2$	THF	ND
4	$(TMP)_2Ag(1/2{\cdot}CO_3)Li_2$	THF	ND	12	$(TMP)_2Ag(CN)Li_2$	Et_2O	31
5	$(TMP)_2Ag(OTf)Li_2$	THF	ND	13[b]	$(TMP)_2Ag(CN)Li_2$	Dioxane	ND
6	$(TMP)_2Ag(CN)Li_2$	THF	99 (92)	14	$(TMP)_2Ag(CN)Li_2$	Benzene	49
7[a]	$(TMP)_2Ag(CN)Li_2$	THF	93	15	$(TMP)_2Ag(CN)Li_2$	Hexane	46
8	$(HMDS)_2Ag(CN)Li_2$	THF	ND	16[c]	$(TMP)_2Ag(CN)Li_2$	THF	99

NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. ND: Not detected. [a] Ag-ate base (0.5 equiv). [b] Deprotonation conducted at room temperature. [c] Exposed to light. TMP: 2,2,6,6-Tetramethylpiperidido. TfO: Trifluoromethanesulfonate. Cy: Cyclohexyl. HMDS: 1,1,1,3,3,3-Hexamethyldisilazido.

The structure of the THF-solvate of $(TMP)_2Ag(CN)Li_2$ **3** was obtained by X-ray crystallography and corroborated by DFT calculations (Fig. 2). Single crystals were obtained from a hexane/toluene solution of the **3** prepared from AgCN and TMPLi in a ratio of 1:2.[17] Complex **3**(THF) has an almost linear –Ag– geometry (176.01(8)°) and the two lithium centers are bridged by cyanide. The resulting lower-order structure mirrors that seen in the corresponding Lipshutz cuprate.[15] However, since the related and yet relatively inert Gilman cuprate[18] is also based on linear, lower-order Cu (like cyanide-free argentate, see ESI Fig. S2), the geometry of the group 11 element cannot alone explain the high reactivity of **3**(THF) in *Do*Ag; the inclusion of LiCN must play a vital role. Overall, the bond lengths and angles in the solid-state structure of **3**(THF) are in good agreement with those obtained by DFT calculation. Meanwhile, preliminary attempts to prove the formation of aryl silver species during our proposed *Do*Ag reactions have been initiated. With this in mind, equimolar reaction between **1a** and **3** has provided evidence for the 1:1 complex of a diarylargentate and bis(TMP)argentate, presumably the result of a disproportionation (Fig. 2d). Further evidence that Gilman-type diarylargentates can form came from the 2:1 reaction of **1a** with **3** (Fig. 2e). Though work is ongoing, the ability of aryl silver species to form in these systems is clear. Moreover, Ag–aryl bond lengths in our initial structures are comparable to those in diarylargentates previously reported by van Koten.[8d]

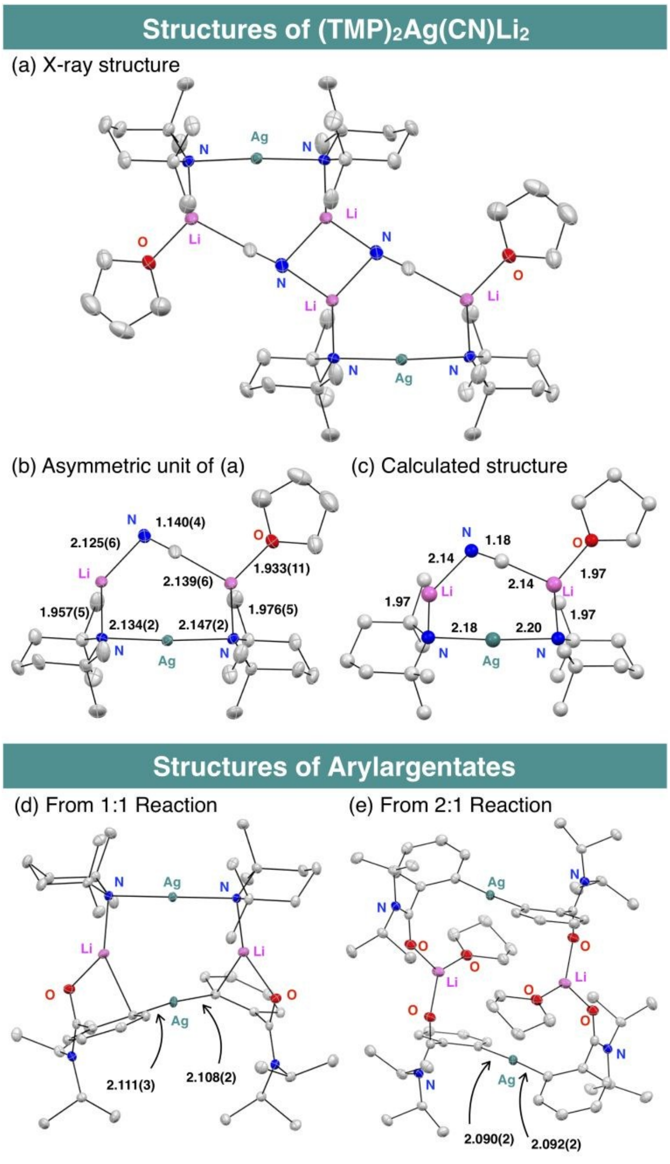


Fig. 2 X-ray and Calculated Structures of **3**(THF). (a) Crystal structure of the dimer of $(TMP)_2Ag(CN)Li_2(THF)$ [**3**(THF)]$_2$; (b) the asymmetric unit (monomer) from (a); (c) the asymmetric unit extracted from the structure of [**3**(THF)]$_2$ calculated at the M06/6-31+G*&LanL2DZ(Ag) level; (d) crystal structure of a diarylargentate adduct obtained by 1:1 reaction of **1a** and **3** and (e) of a diarylargentate dimer from the 2:1 reaction of **1a** and **3**. All crystal structures shown at 30% probability, with H atoms (and THF disorder in (a,b)) omitted. Selected bond lengths in Å.

With the optimized reaction conditions and an understanding of the nature of the base in hand (Table 1, Entry 16 and Fig. 2), we next examined the substrate scope of *Do*Ag (Table 2). We first looked at the choice of DMG. It proved possible to use diethylamide **1b** and morpholine amide **1c**, both of which are chemically more labile than diisopropylamide **1a**. Regioselective argentation of benzonitrile (**1d**) proceeded smoothly in 95% yield, leaving the cyano group intact. Various esters, including CO$_2{}^t$Bu, –^{i}Pr, and –Et, were compatible with the Ag-ate base (**1e**-**1i**). Of considerable importance given that the mechanism of deprotonation in reactions involving the application of **3** is the subject of ongoing study, even methyl ester was tolerated, giving the corresponding iodinated product in high yield (**2h**).[19] Furthermore, traditionally base-susceptible lactones remained intact (**2i**: 99%). The carbonyl group of a ketone also worked as DMG to give the desired product **2j** without any observable side reactions. Benzotrifluoride was also usable; the corresponding iodobenzotrifluoride **2k** was obtained in 56% yield with moderate *ortho* selectivity (78 : 15 : 7 for *ortho* : *meta* : *para*).[20] PhSF$_5$ was also subjected to the DoAg process and argentation took place with perfect *ortho* selectivity (**2l**). Though this reaction needs further optimization, it is remarkable that the metalation proceeded, and this strongly suggests that DoAg could find a role in the diverse functionalization of pharmaceutically important pentafluorosulfanylarenes.[21,22] High ancillary functional group (AFG) tolerance is a key feature of the present argentation reaction. Styrene-type substrate **1m** could be employed without observable polymerization as a side reaction. Halogens and *pseudo*-halogens also survived (**2n**-**2q**). Especially remarkable was the successful retention of the (trifluoromethanesulfonyl)oxy group in **2q**. To our knowledge, this is the first example of this AFG surviving a deprotonative metalation reaction. The highlight of the current development of DoAg is the outstanding chemoselectivity revealed by the first directed *ortho* metalation of a nitroarene by an amidometal ate base. Deprotonative metalation of nitroarenes has been acknowledged for many years to be especially difficult due to incompatibility between the nitro group and strong bases as well as the instability of generated arylmetals.[23] Thus, until now only specific substrates have enabled this chemistry.[24] In contrast, our argentate successfully achieved the conversion of both electron-rich and electron-deficient nitro(hetero)arenes in high yields with perfect regiocontrol next to the nitro group in the presence of other potential DMGs (**2r**-**2t**). Our work has also demonstrated that an aldehyde function is tolerant to the use of our Ag-ate (**2u**).[19,24b-c,25] Heteroarenes such as isoquinoline and indoles, with DMGs at the 2- or 3-positions, were also transformed into the desired products in high yields (**2v**-**2x**). As expected, (TMP)$_2$Ag(CN)Li$_2$ **3** exhibited a stark difference in chemoselectivity in comparison to its cuprous counterpart, (TMP)$_2$Cu(CN)Li$_2$. Upon cupration, sterically unshielded methyl and ethyl esters suffered from uncontrollable side reactions (**2g** and **2h**) and the nitroarene gave only trace amounts of the iodined product **2r** due to the redox activity of Cu.

Table 2 Directed *ortho* Argentation

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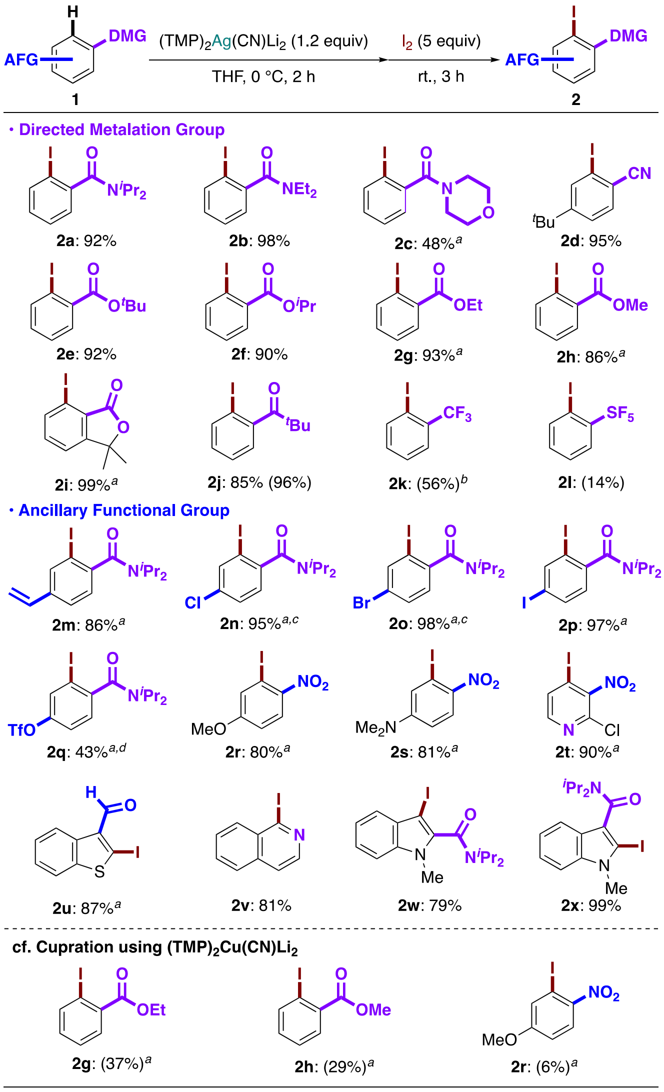
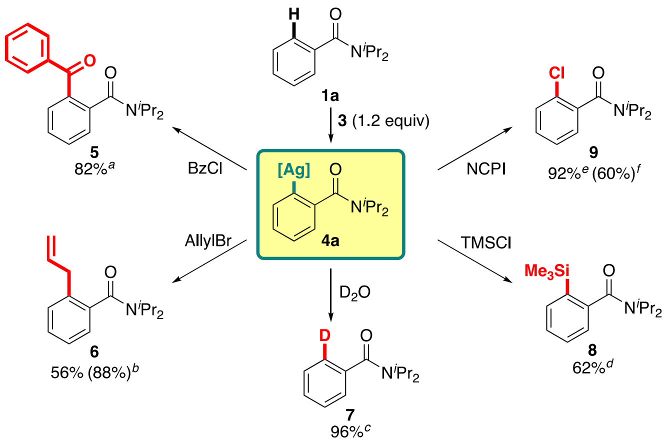


Isolated yields. NMR yields in parentheses, based on mesitylene as an internal standard. [a] Argentation at –40 °C. [b] *ortho* : *meta* : *para* = 78 : 15 : 7. [c] *ortho* : *meta* = >29 : 1. [d] *ortho* : *meta* = 16 : 1.

We next investigated the synthetic use of the putative arylargentate **4a** in aromatic functionalization (Scheme 1). Reactions with benzoyl chloride (**5**), allyl bromide (**6**), D$_2$O (**7**), trimethylsilyl chloride (TMSCl: **8**)[26] and *N*-chlorophthalimide (NCPI: **9**) proceeded well. The reactivity with NCPI was particularly noteworthy, since the alternative use of redox active (TMP)$_2$Cu(CN)Li$_2$ led to significantly less of the desired product on account of undesired oxidative biaryl formation (**9**: 60% and biaryl: 35% NMR yields). Unfortunately, Pd- and Ni-catalyzed cross-coupling reactions[8l-n] have not yet proved successful.



Scheme 1 Reaction Scope of Arylargentate **4a**. Isolated yields. DoAg was conducted with $(TMP)_2Ag(CN)Li_2$ (**3**) (1.2 equiv), 0 °C, 2 h. [a] BzCl (3.5 equiv), 80 °C, 16 h. [b] AllylBr (5.0 equiv), 80 °C, 16 h.; NMR yield in parentheses. [c] D_2O (55 equiv), rt., 16 h.; D/H = 97/3. [d] TMSCl (5.0 equiv), 80 °C, 16 h. [e] DoAg for 0.5 h.; NCPI (3.0 equiv), rt., 1 h. [f] NMR yield when using $(TMP)_2Cu(CN)Li_2$ instead of **3**. Bz: Benzoyl. TMS: Trimethylsilyl. NCPI: *N*-Chlorophthalimide.

Interestingly, putative **4a** is reluctant to react with some typical electrophiles, such as methyl iodide and benzyl bromide (see ESI Table S1). This can be attributed to the high Ag(I→III) redox potential, and results in distinctly different reactivity from the S_N2 processes of organocopper reagents, where the positive charge of the Cu center first increases and then decreases as it goes from Cu(I) to Cu(III) and then back to Cu(I) (Fig. 1).[27]

A study of chalcogen introduction reactions showed that disulfides are excellent substrates for TMP-Ag-ate reaction (Table 3). Unsymmetrically (hetero)arylated sulfides **10a** and **10b** were obtained quantitatively. Excellent chemoselectivity was also observed during reactions with disulfide; benzyl (**10c**), chloro (**10d),** bromo (**10e**), ester (**10f**), and even nitro groups (**10g**) were tolerated, and the corresponding sulfides were obtained in high yields. Taking advantage of the unusual tolerance of the nitro group to our Ag-ate (*vide supra*), the synthesis of diaryl sulfide **10k** with nitro groups on both aryl rings was achieved. In the case of an alkyl substituent, dicyclohexyl disulfide, **10h** was obtained in 54% yield. Diaryl sulfides are important chemical units in medicinal chemistry research.[28] Though the reaction of aryllithium or -magnesium reagents with disulfides can be used to access diaryl sulfides, the yields are variable and the AFG compatibility is low, due to the nature of these organometallics.[29,30] In contrast, our more tolerant argentate-based methodology is a powerful new tool for obtaining diverse diaryl sulfides. Moreover, it allows chalcogen introduction to be extended to the preparation of diaryl selenides and tellurides[31] (**10i** and **10j**).

Table 3 Chalcogen Installation

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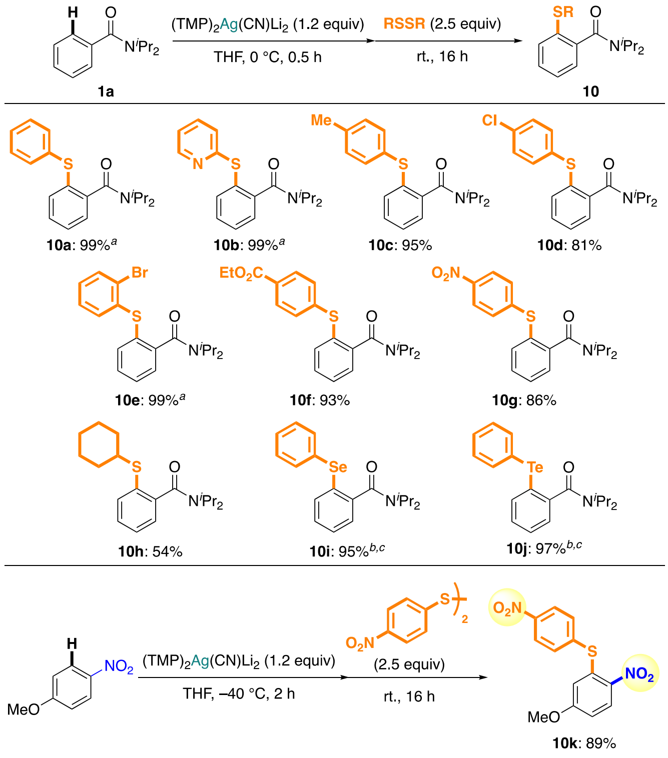

Isolated yields. [a] 40 °C. [b] 80 °C. [c] Chalcogen source (5.0 equiv).

We next focused on the synthesis of azo compounds from diazonium salts. Arylmetals generally react with diazoniums in S_NAr or SET fashion (Sandmeyer-type reaction) and electron-neutral or electron-deficient arenes do not react with diazonium salts by themselves.[32] Minakata's oxidative aniline cross-coupling represents a remarkable advance in this field, albeit with unavoidable formation of the homo-coupled product.[33] We treated **4a** with phenyldiazonium tetrafluoroborate, and obtained the corresponding azo compound **11a** in 68% yield (Table 3). This approach selectively produced heterocoupling products, and cyano, ester, and even nitro groups remained intact during the reaction, affording the corresponding azo compounds with two electron-deficient arenes in high yields (**11b**-**11d**). Aryldiazonium salts without electron-withdrawing groups reacted selectively to give **11e** and **11f**. As expected, reference experiments showed that the arylcuprate prepared from **1a** and $(TMP)_2Cu(CN)Li_2$[16,34] formed biaryl by-products, which strongly suggests that the oxidation of copper competed in this case – something we were able to obviate by using silver.

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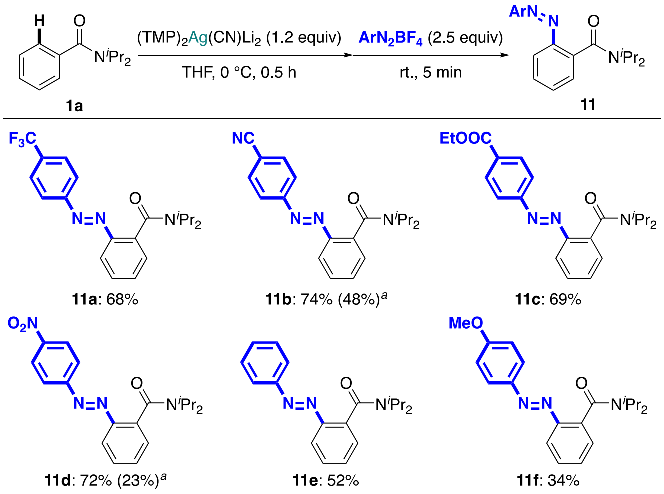
Table 4 Synthesis of Azo Compounds



Azo compounds were isomerized to their *trans* form at 80 °C for 16 h. [a] NMR yield when using (TMP)$_2$Cu(CN)Li$_2$ instead of **3.**

Conclusions

In summary, we have developed a method for the highly chemo- and regioselective deprotonative argentation of a range of (hetero)arenes by designing TMP-Ag-ate base **3**, the structure of which is consistent with its deprotonation efficacy. The resultant putative arylargentate **4a** exhibited excellent reactivity towards electrophiles, including disulfide, diselenide, and ditelluride, with high ancillary functional group tolerance. Deprotonative argentation was also found to be efficient for preparing unsymmetrically substituted azo compounds in combination with diazonium tetrafluoroborates. Further theoretical and spectroscopic studies to expand the reaction scope and to investigate the physicochemical properties of these unique aromatic silver compounds are underway.

Conflicts of interest

There are no conflicts to declare

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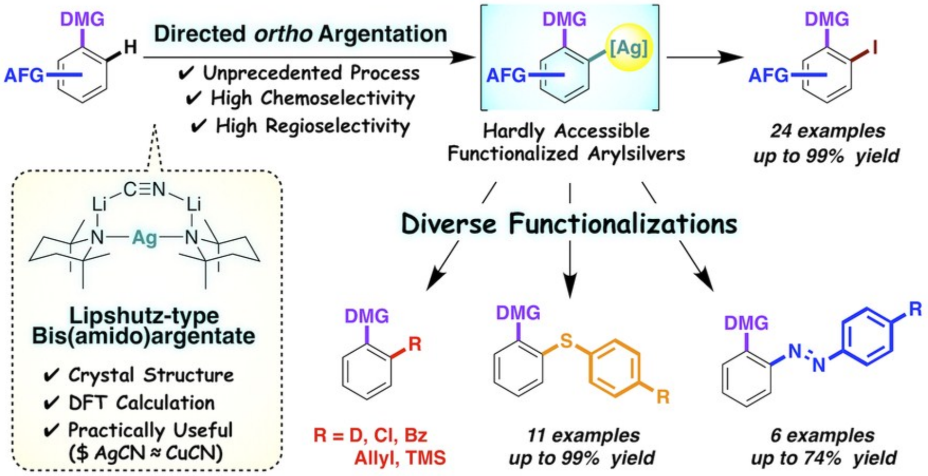

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