Lipshutz-type bis(amido)argentates for directed ortho argentation†

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Bis(amido)argentate (TMP)\textsubscript{2}Ag(CN)Li\textsubscript{2} (3, TMP-Ag-ate; TMP = 2,2,6,6-tetramethylpiperidino) 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)\textsuperscript{1} and coordination geometry. However, whereas organocopper species have opened up many new avenues in organic synthesis, the silver analogues are quite poorly characterized,\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{7} Transmetalation from organometallates to an Ag(i) source is another route offering potential access to the corresponding organosilver species.\textsuperscript{7b,e,n} 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 complexes of a type that have recently received attention as potential reaction intermediates.\textsuperscript{8–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.

Results and discussion

We initially screened Ag-ate bases prepared by combining a range of silver salts and amido ligands for DoAg using \textit{N,N}-diisopropylbenzamide (1a) as a model substrate, followed by

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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 two-fold excess of TMPLi (entries 3-6). (TMP)$_2$Ag(CN)Li$_2$ 3, generated from silver cyanide, uniquely gave the desired product 2a, 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. In contrast to the poor yield obtained with (iPr$_2$N)$_2$Ag(CN)Li$_2$, this result is practically of great importance in terms of cost reduction.$^{13}$ The heteroleptic amidoargentate Me(TMP)Ag(CN)Li$_2$ proved unproductive (entry 11). Lastly, THF was found to be a particularly effective solvent for DoAg (entry 6 vs. entries 12-15).$^{12}$ It is worth noting that neither 3 nor the putative intermediate arylargentate generated was sensitive to light, meaning that all DoAg operations can be conducted without shading tools (entry 16). Based on these data, all subsequent experiments were conducted without special precautions to exclude light.

The structure of the THF-solvate of (TMP)$_2$Ag(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 3 prepared from AgCN and TMPLi in a ratio of 1 : 2.$^{16}$ Complex 3(THF) has an almost linear Ag--geometry (176.01(8)$^\circ$) and the two lithium centers are bridged by cyanide. The resulting lower-order structure mirrors that seen in the corresponding Lishutz cuprate.$^{13}$ However, since the related and yet relatively inert Gilman cuprate$^{14}$ is also based on linear, lower-order Cu (like the cyanide-free argentate, see ESI Fig. S2†), the geometry of the group 11 element cannot alone explain the high reactivity of 3(THF) in DoAg; 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 DoAg 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).

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 DoAg (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$_2$Bu, $^-$Pr, and $^-$Et, were compatible with the Ag 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$_2$ 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 metatation proceeded, and this strongly

| Entry | Ag-ate base | Solvent | Yield (%) | Entry | Ag-ate base | Solvent | Yield (%) |
|-------|------------|---------|-----------|-------|------------|---------|-----------|
| 1     | (TMP)Ag(NO$_3$)Li | THF | ND | 9 | (Pr$_2$N)$_2$Ag(CN)Li$_2$ | THF | 11 |
| 2     | (TMP)Ag(CN)Li | THF | ND | 10 | (Cy$_2$N)$_2$Ag(CN)Li$_2$ | THF | 99 |
| 3     | (TMP)$_2$Ag(NO$_3$)Li$_2$ | THF | ND | 11 | Me(TMP)Ag(CN)Li$_2$ | THF | ND |
| 4     | (TMP)$_2$Ag(1/2 CO$_2$)Li$_2$ | THF | ND | 12 | (TMP)$_2$Ag(CN)Li$_2$ | Et$_2$O | 31 |
| 5     | (TMP)$_2$Ag(OtBu)Li$_2$ | THF | ND | $^{13}^a$ | (TMP)$_2$Ag(CN)Li$_2$ | Dioxiane | ND |
| 6     | (TMP)$_2$Ag(CN)Li$_2$ | THF | 99 (92) | 14 | (TMP)$_2$Ag(CN)Li$_2$ | Benzene | 49 |
| $^g$  | (TMP)$_2$Ag(CN)Li$_2$ | THF | 93 | 15 | (TMP)$_2$Ag(CN)Li$_2$ | Hexane | 46 |
| 8     | (HMDS)$_2$Ag(CN)Li$_2$ | THF | ND | $^{16}^d$ | (TMP)$_2$Ag(CN)Li$_2$ | THF | 99 |

$^a$ NMR yields based on mesitylene as an internal standard. Isolated yield in parentheses. ND: not detected. $^b$ Ag-ate base (0.5 equiv.). $^c$ Deprotonation conducted at room temperature. $^d$ Exposed to light. TMP: 2,2,6,6-tetramethylpiperidido. TFO: trifluoromethanesulfonato. Cy: cyclohexyl. HMDS: 1,1,1,3,3,3-hexamethyldisilazido.
suggests that DoAg could find a role in the diverse functionalization of pharmaceutically important pentfluorosulfanylarenes. 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 metation reaction. The highlight of the current development of DoAg is the outstanding chemoselectivity revealed by the first directed ortho metation of a nitroarene by an amidometal ate base. Deprotonative metation 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. Thus, until now only specific substrates have enabled this chemistry. 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). Heteroarenes such as isoquinoline and indoles, with DMGs at the 2-and 3-positions, were also transformed into the desired products in high yields (2v–2x). As expected, (TMP)2Ag(CN)Li2 3 exhibited a stark difference in

![Fig. 2 X-ray and calculated structures of argentates. (a) Crystal structure of the dimer of (TMP)2Ag(CN)Li2(THF)](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 atomic displacement parameters in crystal structures shown at 30% probability, with H atoms (and THF disorder in (a and b)) omitted. Selected bond lengths in Å.

![Table 2. Directed ortho argention](a)

| DMG | (TMP)2Ag(CN)Li2 (1.2 equiv) | THF, 0 °C, 2 h | L2 (5 equiv) | n, 3 h | Yield (%) |
|-----|-----------------------------|----------------|-------------|-------|----------|
| 1a  | 1b                          |                |             |       | 92%      |
| 1m  | 1n                          |                |             |       | 90%      |
| 1o  | 1p                          |                |             |       | 95%      |
| 1q  | 1r                          |                |             |       | 85%      |
| 1s  | 1t                          |                |             |       | 56%      |
| 1u  | 1v                          |                |             |       | 97%      |
| 1w  | 1x                          |                |             |       | 81%      |
| 1y  | 1z                          |                |             |       | 79%      |
| 1z  | 1aa                         |                |             |       | 90%      |
| 2a  | 2b                          |                |             |       | 37%      |
| 2m  | 2n                          |                |             |       | 80%      |
| 2o  | 2p                          |                |             |       | 81%      |
| 2r  | 2q                          |                |             |       | 90%      |

a Isolated yields. NMR yields in parentheses, based on mesitylene as an internal standard. b Argentation at –40 °C. c Ortho : meta : para = 78 : 15 : 7. d Ortho : meta = 29 : 1. e Ortho : meta = 16 : 1.
chemoselectivity in comparison to its cuprous counterpart, \((\text{TMP})_2\text{Cu(CN)Li}_2\). 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 iodinated product 2r due to the redox activity of Cu.

We next investigated the synthetic use of the putative arylargentate 4a in aromatic functionalization (Scheme 1). Reactions with benzoyl chloride (5), allyl bromide (6), \(\text{D}_2\text{O}\) (7), trimethylsilyl chloride (TMSCl) (see ESI Table S1†) and N-chlorophthalimide (NCPI: 9) proceeded well. The reactivity with NCPI was particularly noteworthy, since the alternative use of redox active \((\text{TMP})_2\text{Cu(CN)Li}_2\) 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\(^{16-19}\) have not yet proved successful.

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 \(\rightarrow\) III) redox potential, and results in distinctly different reactivity from the \(\text{S}_2\text{Ar}\) 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(ii) and then back to Cu(i).\(^{20}\)

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.\(^{21}\)

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.\(^{22,23}\) 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\(^{11}\) (10i and 10j).

We next focused on the synthesis of azo compounds from diazonium salts. Arylmetals generally react with diazoniums in \(\text{S}_2\text{Ar}\) or SET fashion (Sandmeyer-type reaction) and electron-neutral or electron-deficient arenes do not react with diazonium salts by themselves.\(^{24}\) Minakata’s oxidative aniline cross-coupling represents a remarkable advance in this field, albeit with unavoidable formation of the homo-coupled product.\(^{25}\) We treated 4a with phenyldiazonium tetrafluoroborate, and obtained the corresponding azo compound 11a in 68% yield (Table 4). 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 \((\text{TMP})_2\text{Cu(CN)Li}_2\) 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.

### Table 3 Chalcogen installation

| Scheme 1 Reaction scope of arylargentate 4a | Isolated yields. | \(40\ ^\circ\text{C}\). | \(80\ ^\circ\text{C}\). | Chalcogen source (5.0 equiv.) |
|---|---|---|---|---|
| | 1a | 82% | \(2\ ^\circ\text{C}\). | \(\text{D}_2\text{O}\) (55 equiv.), \(\text{rt.}\), 16 h. |
| | 2a | 66% | \(\text{D}_2\text{O}\) (55 equiv.), \(\text{rt.}\), 16 h. | \(\text{D}_2\text{O}\) (1.2 equiv.), \(\text{rt.}\), 16 h. |
| | 3a | 92%* | \(\text{NMR yield}\). | \(\text{NCPI (3.0 equiv.)}, \text{rt.}\), 1 h. |
| | 4a | 90% | \(\text{NMR yield}\) when using \((\text{TMP})_2\text{Cu(CN)Li}_2\) instead of 3. | 80% D/H = 97/3. |

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Table 4  Synthesis of azo compounds

![Synthesis of azo compounds](image)

**Notes and references**

1. RIKEN Integrated Cluster of Clusters (RICC), HOKUSAI-GreatWave and HOKUSAI-BigWaterfall provided the computer resources for the DFT calculations.

**Conflicts of interest**

There are no conflicts to declare.

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