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Deprotonative Magnesation and Cadmation of [1,2,3]Triazolo[1,5-*a*]pyridines

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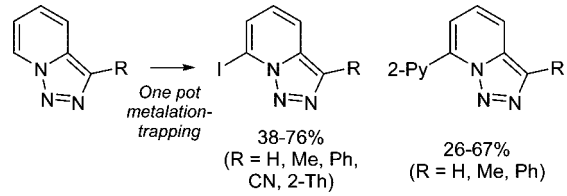

[1,2,3]Triazolo[1,5-*a*]pyridine and 3-substituted derivatives were regioselectively metalated at the 7 position using either Bu_3MgLi or $(TMP)_3CdLi$, the former at −10 °C and the latter at room temperature. The lithium arylmagnesates (R = H, Me, Ph) proved to react with iodine (34−75%) or 3,4,5-trimethoxybenzaldehyde (32−51%). Attempts to obtain the cross-coupling products using 2-bromopyridine under palladium catalysis failed, a result attributed to the low stability of these compounds. The corresponding lithium arylzincates reacted in 17−60% yield under the same reaction conditions. The lithium arylcadmates were either trapped with iodine (38−76%, R = H, Me, Ph, CN, 2-thienyl) or involved in palladium-catalyzed cross-coupling reactions with 2-bromopyridine (26−67%, R = H, Me, Ph). For R = 2-pyridyl, 3-(6-iodo-2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine was isolated in 73% yield. $(TMP)_3CdLi$ also proved suitable for the clean dideprotonation of two substrates (R = H, 2-thienyl), a result demonstrated by quenching with iodine (66−75%).

Introduction

The deprotonative metalation of aromatic rings has been widely used as a powerful method for regioselective functionalization. The methodology using alkyllithiums and lithium dialkylamides has been largely employed for this purpose.[1] Nevertheless, their use is limited to substrates with C−H acidity enhanced by directing groups and generally requires low reaction temperatures due to the high reactivity of the corresponding aryllithiums. In addition, unlike organoboron, organotin, organozinc, and organomagnesium compounds, organolithiums hardly can be involved in cross-coupling reactions.[2]

Mixed alkaline organobimetallic mixtures such as those described by Schlosser[3] and Lochmann[4] exhibit powerful basic properties that cannot be attained by the homometallic compounds on their own but can be obtained by low chemoselectivities. Organobimetallic mixtures containing only one alkali atom display a large panel of reactivities depending on both the nonalkali metal and the groups connected to it. R_nMLi-type

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(1) For excellent general reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (c) Schlosser, M. *Organometallics in Synthesis*, 2nd ed.; Wiley: New York, 2002; *Chapter 1*. For more specific reviews concerning π-deficient heterocycles, see: (d) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187–304. (e) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090. (f) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489–4505. (g) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161–1172. (h) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595–609.

(2) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
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(4) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115–1126.

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ate compounds, which are present in stoichiometric[5] or catalytic[6] amounts in these mixtures, in general are supposed to be responsible for the exhibited reactivities ("synergy").

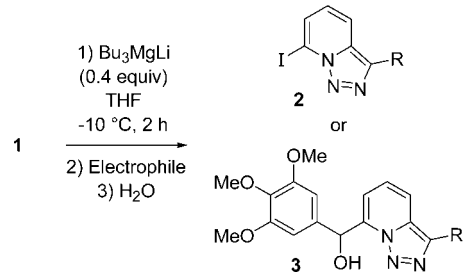
In the framework of studies dealing with triazolopyridine systems,[7] we have been interested in the development of new strategies to functionalize [1,2,3]triazolo[1,5-*a*]pyridines. Among the methods used,[8] deprotonative metalation reactions using lithium bases have been developed and prove efficient in the absence of reactive functional groups, provided that very low reaction temperatures are used.

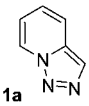
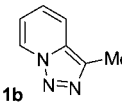
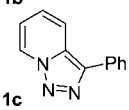
Herein, we report the first regio-controlled functionalization of [1,2,3]triazolo[1,5-*a*]pyridines using lithium−magnesium and lithium−cadmium organobimetallic bases.

Results and Discussion

To develop new deprotonation reactions of [1,2,3]triazolo[1,5-*a*]pyridines, our approach first capitalized on the good reactivity of magnesates. Since 1999, Mulvey has documented the preparation of mixed alkali metal−magnesium amides for the site selective deprotonation of benzene,[9] toluene,[10] ferrocene,[11] ruthenocene,[12] osmocene,[12] bis(arene)chromium,[13] and furan.[14] At the same time, we studied the deprotonative metalation of pyridines,[15] thiophenes,[16] oxazoles,[17] and furans[18] using easily available lithium magnesates, with the obtained arylmagnesates being either trapped with electrophiles or involved in palladium-catalyzed cross-couplings.

TABLE 1. Deprotonation of 1a−c Using Bu_3MgLi (0.4 equiv) Followed by Electrophilic Trapping



entry	substrate	product (R)	yield (%)
1	 1a	**2a** (H)	34
2		**3a** (H)	32
3	 1b	**2b** (Me)	40 (23)[a]
4		**3b** (Me)	61 (60)[b]
5	 1c	**2c** (Ph)	75
6		**3c** (Ph)	51

[a] Reaction was carried out using BuLi and THF at −40 °C.[27] [b] Reaction was carried out in the presence of TMEDA (0.4 equiv).

The first studies of the lithiation of [1,2,3]triazolo[1,5-*a*]-pyridine (**1a**) were reported in 1980 and showed that butyllithium and lithium diisopropylamide (LiDA) are suitable for a regioselective metalation at the 7 position when used in ethereal solvents (the best yields being obtained in tetrahydrofuran), provided that the reaction temperature is kept below −40 °C.[19] Similar reaction conditions can be used for 3-methyl and 3-phenyl derivatives **1b**,**c**.[19] Above this temperature, the corresponding 7,7′-dimers form.[20] Metalation yields were improved in 1987 by using butyllithium in toluene at −40 °C.[21]

The deprotonation of [1,2,3]triazolo[1,5-*a*]pyridine[22] (**1a**) was attempted using $^1/_3$ equiv of lithium tributylmagnesate[23] (Bu_3MgLi) in THF at −10 °C. Addition to the reaction mixture of iodine and 3,4,5-trimethoxybenzaldehyde after 2 h afforded iodide **2a**[24] and alcohol **3a**, respectively, in moderate yields (Table 1, entries 1 and 2). When treated under the same reaction

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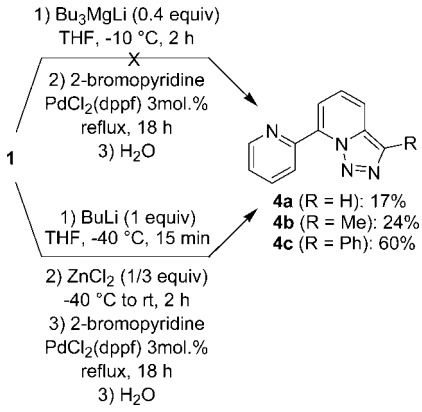
SCHEME 1. Deprotonation of 1a−c Followed by Cross-Coupling

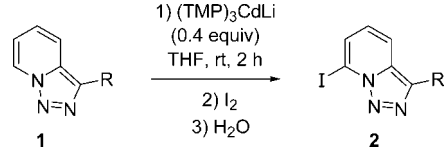


conditions, 3-methyl[25] and 3-phenyl[26] derivatives **1b**,**c** furnished the corresponding iodides **2b**,**c** and alcohols **3b**,**c** in better yields ranging from 40 to 75% (Table 1, entries 3−6). Because heterocycles are more efficiently deprotonated using Bu_3MgLi in THF-containing TMEDA,[16] a reaction involving 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine (**1b**) was attempted with this change but without improvement.

In order to synthesize bisheterocycles, cross-coupling reactions between the [1,2,3]triazolo[1,5-*a*]pyridines **1a**,**b** magnesates and 2-bromopyridine were attempted under palladium catalysis using 1,1′-bis(diphenylphosphino)ferrocene (dppf) as the ligand[28] but without success. To know if this result could be related to the moderate stability of the heterocyclic organomagnesium compounds, we decided to involve the corresponding lithium zincates in similar reactions.[29] For this purpose, the [1,2,3]triazolo[1,5-*a*]pyridines **1a**−**c** were successively treated with butyllithium in tetrahydrofuran at −40 °C for 15 min[30] and zinc chloride ($^1/_3$ equiv) before heating with 2-bromopyridine in the presence of the catalyst. This protocol allowed compounds **4a**−**c** to be obtained in yields ranging from 17 to 60% (Scheme 1).

In order to avoid butyllithium, which hardly tolerates functional groups and requires low temperatures that can be difficult to realize on an industrial scale, we investigated the deprotometalation using a still efficient but more chemoselective ate compound. By combination of LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) with soft organometallic compounds, ate bases such as $^tBu_2Zn(TMP)Li$,[29f,31] $^tBu_3Al(TMP)Li$,[32] $(Me_3SiCH_2)_2$-Mn(TMP)Li·TMEDA,[33] and MeCu(TMP)$(CN)Li_2$[34] have been prepared and used to generate functionalized aromatic compounds. When performed in tetrahydrofuran (THF), the reactions proved to be chemoselective but require 1 or 2 equiv of base. We reported recently a new basic mixture ("TMP-cadmate"), prepared by mixing LiTMP (3 equiv) and $CdCl_2$·TMEDA,[35] that combines both efficiency and chemoselectivity.[36] The method based on the handling of cadmium salts, for which the toxicity is reported,[37] was used for the functionalization of the sensitive [1,2,3]triazolo[1,5-*a*]pyridines.

TABLE 2. Deprotonation of 1a−f Using In-Situ-Prepared $(TMP)_3CdLi$ (0.4 equiv)[a] Followed by Trapping with I_2



1 2

entry	1	R	product	yield (%)
1	**1a**	H	**2a**	72
2	**1b**	Me	**2b**	76[a] (23)[b]
3	**1c**	Ph	**2c**	71
4	**1d**	CN	**2d**	65
5	**1e**	2-pyridyl	**2e** → **2′e**	73 (49)[c]
6	**1f**	2-thienyl	**2f**	38

[a] One equivalent of base was used for substrate **1b**. [b] Reaction was carried out using using BuLi and THF at −40 °C.[27] [c] Reaction was carried out using LiDA and THF at −40 °C.[40]

When substrates **1a** and **1c** were successively treated by in-situ-prepared $(TMP)_3CdLi$ (0.4 equiv) in THF at rt for 2 h and iodine, the expected iodides **2a** and **2c** were provided in 71−72% yields (Table 2, entries 1 and 3). The iodide **2b** was obtained similarly from **1b** in 76% yield (Table 2, entry 2) but by using $(TMP)_3CdLi$ (1 equiv). These satisfying results encouraged us to attempt the reaction with more elaborate substrates.

Thus, we turned to 3-cyano-[1,2,3]triazolo[1,5-*a*]pyridine[38] (**1d**) for which the deprotolithiation only gives a complex

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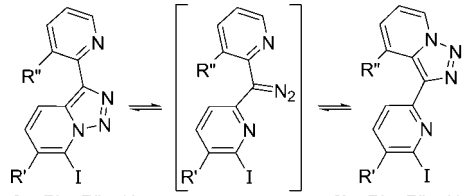
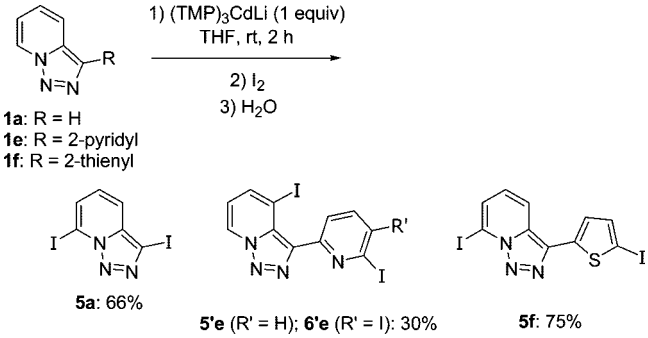
(37) The use of salts reduces the risk of cadmium absorption: Haddad, L. M.; Shannon, M.; Winchester, J. F. *Clinical Management of Poisoning and Drug Overdose*, 3rd ed.; Saunders: Philadelphia, 1998.

SCHEME 2. Isomerization of 7-Iodo-3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridines 2e, 5e, and 6e



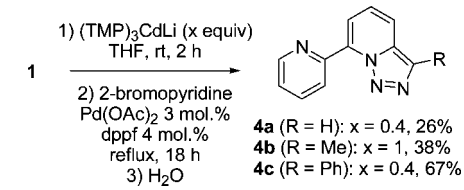
SCHEME 3. Polydeprotonation of 1a, 1e, and 1f Using In-Situ-Prepared (TMP)$_3$CdLi (1 equiv) Followed by Trapping with I$_2$



mixture of derivatives.[38] When submitted successively to the mixed lithium−cadmium base and iodine under the conditions used for **1a**−**c**, the expected iodide **2d**[39] was isolated in a satisfying 65% yield (Table 2, entry 4). Both 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine (**1e**) and 3-(2-thienyl)-[1,2,3]triazolo[1,5-*a*]pyridine (**1f**) have previously been metalated using LiDA in THF.[40] The protocol developed here allowed the iodides **2′e** and **2f** to be obtained (Table 2, entries 5 and 6). The formation of **2′e**[39] instead of expected **2e** can be rationalized as previously reported (Scheme 2).[40]

Because the basic mixture "TMP-cadmate" is able to dideprotonate substrates such as pyrazine, thiazole, *N*-Boc pyrrole, and thiophenes,[36] we decided to attempt to access the diiodo derivatives of [1,2,3]triazolo[1,5-*a*]pyridines using 1 equiv of base. Starting from **1a**, the 3,7-diiodo derivative **5a** was isolated in 66% yield (Scheme 3). Unexpectedly, a mixture of diiodide **5′e** and triiodide **6′e**,[41] from which the latter was isolated in 30% yield, was obtained from **1e** using the same protocol. Iodides **5′e** and **6′e** probably resulted from isomerization of compounds **5e** and **6e** as described above (Scheme 2). Precursor **5e** could be formed by dideprotonation at both 7 (the more-activated position of [1,2,3]triazolo[1,5-*a*]pyridine) and 3′ (induced by the neighboring triazole ring) positions.[42] Triiodide

SCHEME 4. Deprotonation of 1a−c Using In-Situ-Prepared (TMP)$_3$CdLi (*x* equiv) Followed by Cross-Coupling



6e could be generated by metalation of **5e** during the trapping with iodine (excess of base). The formation of diiodide **5f** is less unexpected and logically results from a dideprotonation at the more-activated positions of the [1,2,3]triazolo[1,5-*a*]pyridine and thiophene rings (Scheme 3).

Even if cross-coupling reactions using cadmium compounds mostly have been described starting from organocadmium chlorides,[43] reactions from substrates **1a**−**e** were attempted. Preliminary results[36] showing palladium catalysis using dppf as the ligand were appropriate, and the metalated intermediates were subjected to reaction with 2-bromopyridine at the reflux temperature of THF. Whereas no reaction was observed in the presence of an electron-withdrawing group at the 3 position of the [1,2,3]triazolo[1,5-*a*]pyridine ring (substrates **1d**,**e**) under these conditions, the bis(heterocycles) **4a**−**c** were isolated in yields ranging from 26 to 67% (Scheme 4).

Conclusion

Modification of organometallic compounds in order to get more chemoselective bases for the deprotonation of sensitive substrates is a challenging area. Combining lithium and magnesium organometallics in lithium triorganomagnesate (Bu_3MgLi) resulted in good chemoselectivity when compared to those of lithium bases, allowing reactions to be carried out in similar yields at −10 °C instead of −40 °C when using classical lithium bases.[19a,21a,27,40,44] Using cadmium instead of magnesium and TMP instead of butyl groups afforded an efficient and chemoselective base, which was able to regioselectively deprotonate [1,2,3]triazolo[1,5-*a*]pyridines substituted or not at the 3 position. Polydeprotonation also proved possible in some cases. The heterocyclic lithium cadmates were evidenced using iodine as an electrophile. Trapping also was attempted using 2-bromopyridine to give the expected coupling products under palladium catalysis. Compared to the previously described methods for the synthesis of similar bisheterocycles,[7d,45] the procedure described here has the advantage of being "one pot" from the corresponding triazolopyridines.

Because of the toxicity of cadmium compounds,[37] we actually tried diligently to develop basic mixtures containing cadmium salts as catalysts. We already observed, using anisole as a substrate, that (TMP)$_3$CdLi did not behave as an efficient catalyst when the reaction was performed using a mixture of LiTMP (1.5 equiv) and $ZnCl_2$·TMEDA (0.5 equiv) in THF at rt,[46] but other catalysis experiments are under investigation. Parallel investigations are underway in order to develop new mixed

(38) For the synthesis and a previously described study of the deprotolithiation of substrate **1d**, see: Jones, G.; Mouat, D. J.; Pitman, M. A. *Tetrahedron* **1995**, *51*, 10969–10978.

(39) The structures of **2d** and **2′e** were determined by NMR and confirmed by X-ray diffraction analysis (see presented ORTEP figure in Supporting Information).

(40) For the synthesis and deprotolithiation of substrates **1e** and **1f**, see ref 20b. For the deprotolithiation of substrate **1e** (notably followed by trapping with iodine), see also: Abarca, B.; Alkorta, I.; Ballesteros, B.; Blanco, F.; Chadlaoui, M.; Elguero, J.; Mojarrad, F. *Org. Biomol. Chem.* **2005**, *3*, 3905–3910. Note that substrate **1e** is now commercially available (ASM Research Chemicals).

(41) The structure of **6′e** was determined by NMR (NOESY, HMBC, and HMQC experiments).

(42) Concerning metalation induced by an aza aromatic substituent, see: Mongin, F.; Rebstock, A.-S.; Trécourt, F.; Quéguiner, G.; Marsais, F. *J. Org. Chem.* **2004**, *69*, 6766–6771, and references cited therein.

(43) (a) Negishi, E.-i.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393–2401. (b) Bumagin, N. A.; Ponomarev, A. B.; Beletskaya, I. P. *Zh. Org. Khim.* **1987**, *23*, 1345–1353. See also: (c) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275–7278.

(44) Abarca, B.; Ballesteros, R.; Elmasnaouy, M.; D'Ocón, P.; Ivorra, M. D.; Valiente, M. *ARKIVOC (Gainesville, FL, U.S.)* **2002**, (x), 9–13.

(45) Abarca, B.; Ballesteros, R.; Blanco, F.; Bouillon, A.; Collot, V.; Domínguez, J. R.; Lancelot, J. C.; Rault, S. *Tetrahedron* **2004**, *60*, 4887–4893.

lithium−metal bases of the ate type that are still efficient and chemoselective but less toxic.

Experimental Section

General Procedure A (Deprotonation Using 0.4 equiv of Bu_3MgLi Followed by Trapping Using I_2). To a stirred, cooled (−10 °C), and freshly prepared solution of $MgBr_2$[47] (0.8 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 2.4 mmol) and 1 h later the substrate (2.0 mmol). After 2 h at this temperature, a solution of I_2 (0.61 g, 2.4 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure A′ (Deprotonation Using 0.4 equiv of Bu_3MgLi Followed by Trapping Using 3,4,5-Trimethoxybenzaldehyde). To a stirred, cooled (−10 °C), and freshly prepared solution of $MgBr_2$[47] (0.8 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 2.4 mmol) and 1 h later the substrate (2.0 mmol). After 2 h at this temperature, 3,4,5-trimethoxybenzaldehyde (0.48 g, 2.4 mmol) was added. The mixture was stirred overnight before addition of water (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure B (Deprotonation Using 0.4 equiv of $CdCl_2$·TMEDA and 1.2 equiv of LiTMP Followed by Trapping Using I_2). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.42 mL, 2.4 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 2.4 mmol) and 5 min later $CdCl_2$·TMEDA[35] (0.24 g, 0.8 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at rt, a solution of I_2 (0.61 g, 2.4 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure C (Deprotonation Using 1.0 equiv of $CdCl_2$·TMEDA and 3.0 equiv of LiTMP Followed by Trapping Using I_2). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.1 mL, 6.0 mmol) in THF (5 mL) were successively added BuLi (1.6 M hexanes solution, 6.0 mmol) and 5 min later $CdCl_2$·TMEDA[35] (0.60 g, 2.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at rt, a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

General Procedure D (Deprotonation Using 1 equiv of BuLi Followed by Transmetalation Using $ZnCl_2$ and Cross-Coupling). To a stirred, cooled (−40 °C) solution of the substrate (2.0 mmol) in THF (4 mL) were added BuLi (1.6 M hexanes solution, 2.4 mmol) and 15 min later a solution of $ZnCl_2$ (0.12 g, 0.8 mmol) in THF (3 mL). After 2 h at rt, the mixture thus obtained was added dropwise to a solution of 2-bromopyridine (0.19 mL, 2.0 mmol) and $PdCl_2$(dppf) (49 mg, 60 μmol), and the resulting mixture was heated at reflux for 18 h before addition of water saturated with NH_4Cl (0.5 mL) and AcOEt (30 mL). After drying over $MgSO_4$, the organic phase was filtered and concentrated under reduced pressure.

General Procedure E (Deprotonation Using 0.4 equiv of $CdCl_2$·TMEDA and 1.2 equiv of LiTMP Followed by Cross-Coupling). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.42 mL, 2.4 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 2.4 mmol) and 5 min later $CdCl_2$·TMEDA[35] (0.24 g, 0.8 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at rt, the mixture was treated with $Pd(OAc)_2$ (13 mg, 60 μmol), dppf (44 mg, 80 μmol), and 2-bromopyridine (0.19 mL, 2.0 mmol). The mixture was heated under reflux for 18 h before addition of water (0.5 mL) and AcOEt (30 mL). After drying over $MgSO_4$, the organic phase was filtered and concentrated under reduced pressure.

General Procedure E′ (Deprotonation Using 1 equiv of $CdCl_2$·TMEDA and 3 equiv of LiTMP Followed by Cross-Coupling). To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.1 mL, 6.0 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 6.0 mmol) and 5 min later $CdCl_2$·TMEDA[35] (0.60 g, 2.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at rt, the mixture was treated with $Pd(OAc)_2$ (13 mg, 60 μmol), dppf (44 mg, 80 μmol), and 2-bromopyridine (0.19 mL, 2.0 mmol). The mixture was heated under reflux for 18 h before addition of water (0.5 mL) and AcOEt (30 mL). After drying over $MgSO_4$, the organic phase was filtered and concentrated under reduced pressure.

7-Iodo-[1,2,3]triazolo[1,5-*a*]pyridine (2a). 2a was obtained according to general procedure A (0.17 g, 34%) or B (0.35 g, 72%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 95:5) as a white powder. Mp: 148−150 °C. ^{1}H NMR ($CDCl_3$): δ 6.99 (dd, 1H, J = 8.5, 7.2 Hz), 7.46 (d, 1H, J = 6.9 Hz), 7.72 (d, 1H, J = 8.8 Hz), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 86.0 (C), 117.8 (CH), 126.1 (CH), 127.3 (CH), 127.7 (CH), 134.3 (C). IR (KBr) ν: 1618, 1533, 1480, 1410, 1350, 1308, 1298, 1261, 1228, 1204, 1144, 1095, 1036, 970, 932, 802, 780, 722, 677, 630, and 580 cm^{-1}. HRMS: calcd for $C_6H_4IN_3$ ($M^{+\bullet}$) 244.9450, found 244.9406. Anal. Calcd for $C_6H_4IN_3$ (245.02): C, 29.41; H, 1.65; N, 17.15. Found: C, 29.05; H, 1.99; N, 17.13.

7-Iodo-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine (2b). 2b was obtained according to general procedure A (0.21 g, 40%) or C (0.39 g, 76%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 80:20) as a beige powder. Mp: 135 °C. ^{1}H NMR ($CDCl_3$): δ 2.59 (s, 3H), 6.92 (t, 1H, J = 7.8 Hz), 7.41 (d, 1H, J = 6.8 Hz), 7.60 (d, 1H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$): δ 11.0 (CH_3), 86.0 (C), 117.4 (CH), 124.5 (CH), 127.0 (CH), 132.3 (C), 136.6 (C); IR (KBr) ν: 3066, 2962, 2922, 1622, 1532, 1505, 1458, 1428, 1397, 1335, 1298, 1261, 1225, 1203, 1127, 1103, 1035, 925, 806, 768, 722, 672, 610, 551, and 497 cm^{-1}. HRMS: calcd for $C_7H_6IN_3$ ($M^{+\bullet}$) 258.9606, found 258.9586. Anal. Calcd for $C_7H_6IN_3$ (259.05): C, 32.46; H, 2.33; N, 16.22. Found: C, 32.66; H, 2.49; N, 15.82.

7-Iodo-3-phenyl-[1,2,3]triazolo[1,5-*a*]pyridine (2c). 2c was obtained according to general procedure A (0.48 g, 75%) or B (0.46 g, 71%) and isolated after purification by flash chromatography on silica gel (heptane/CH_2Cl_2 50:50) as a yellow powder. Mp: 139 °C. ^{1}H NMR ($CDCl_3$): δ 7.03 (dd, 1H, J = 8.8, 7.0 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.47−7.52 (m, 3H), 7.91−7.98 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 86.6 (C), 118.2 (CH), 126.3 (CH), 126.9 (2CH), 127.4 (CH), 128.2 (CH), 129.1 (2CH), 131.2 (C), 131.5 (C), 140.0 (C). IR (KBr) ν: 3087, 3052, 1614, 1509, 1484, 1448, 1418, 1345, 1291, 1267, 1215, 1184, 1134, 1073, 1039, 1007, 929, 804, 789, 767, 729, 696, 688, 610, and 538 cm^{-1}. HRMS: calcd for $C_{12}H_8IN_3$ ($M^{+\bullet}$) 320.9763, found 320.9763. Anal. Calcd for $C_{12}H_8IN_3$ (321.12): C, 44.88; H, 2.51; N, 13.09. Found: C, 44.59; H, 2.56; N, 12.99.

3-Cyano-7-iodo-[1,2,3]triazolo[1,5-*a*]pyridine (2d). 2d was obtained according to general procedure B (0.35 g, 65%) and isolated after purification by flash chromatography on silica gel

(46) Concerning the use of $ZnCl_2$·TMEDA/LiTMP (1:3) to deprotonate, see: (a) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602–6605. (b) Seggio, A.; Lannou, M.-I.; Chevallier, F.; Nobuto, D.; Uchiyama, M.; Golhen, S.; Roisnel, T.; Mongin, F. *Chem.−Eur. J.* **2007**, *13*, 9982–9989. (c) L'Helgoual'ch, J.-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177–183.

(47) Meth-Cohn, O.; Jiang, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3737–3745.

(CH_2Cl_2) as a white powder. Mp: 202 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ 7.51 (t, 1H, J = 7.8 Hz), 7.92 (d, 1H, J = 6.9 Hz), 8.18 (d, 1H, J = 8.6 Hz). ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, 1H, J = 8.8, 7.2 Hz), 7.60 (dd, 1H, J = 7.1, 0.9 Hz), 7.83 (dd, 1H, J = 8.7, 0.9 Hz). ^{13}C NMR [$(CD_3)_2SO$]: δ 91.8 (C), 112.0 (C), 112.6 (C), 116.3 (CH), 129.1 (CH), 131.6 (CH), 137.0 (C). Anal. Calcd for $C_7H_3IN_4$ (270.03): C, 31.14; H, 1.12; N, 20.75. Found: C, 31.20; H, 1.21; N, 20.54.

3-(6-Iodo-2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine (2′e).[40] **2′e** was obtained according to general procedure B (0.47 g, 73%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 80:20) as a beige powder. Mp: 191 °C. ^{1}H NMR ($CDCl_3$): δ 7.06 (td, 1H, J = 6.8, 0.8 Hz), 7.37−7.44 (m, 2H), 7.60 (d, 1H, J = 7.6 Hz), 8.27 (d, 1H, J = 7.8 Hz), 8.59 (d, 1H, J = 8.9 Hz), 8.74 (d, 1H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 116.2 (CH), 117.4 (C), 119.2 (CH), 121.0 (CH), 125.4 (CH), 127.1 (CH), 132.2 (C), 132.8 (CH), 135.9 (C), 138.2 (CH), 153.2 (C). Anal. Calcd for $C_{11}H_7IN_4$ (322.10): C, 41.02; H, 2.19; N, 17.39. Found: C, 40.98; H, 2.32; N, 17.52.

7-Iodo-3-(2-thienyl)-[1,2,3]triazolo[1,5-*a*]pyridine (2f). 2f was obtained according to general procedure B (0.25 g, 38%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 80:20) as a beige powder. Mp: 134 °C. ^{1}H NMR ($CDCl_3$): δ 6.95 (dd, 1H, J = 8.8, 7.0 Hz), 7.05 (dd, 1H, J = 5.0, 3.6 Hz), 7.28 (dd, 1H, J = 5.0, 1.0 Hz), 7.38 (dd, 1H, J = 6.9, 0.8 Hz), 7.45 (dd, 1H, J = 3.6, 1.0 Hz), 7.85 (dd, 1H, J = 8.9, 0.8 Hz). ^{13}C NMR ($CDCl_3$): δ 86.6 (C), 118.1 (CH), 124.4 (CH), 125.5 (CH), 126.4 (CH), 127.6 (CH), 127.9 (CH), 130.4 (C), 133.3 (C), 135.5 (C). Anal. Calcd for $C_{10}H_6IN_3S$ (327.14): C, 36.71; H, 1.85; N, 12.84; S, 9.80. Found: C, 36.46; H, 1.98; N, 12.41; S, 10.08.

([1,2,3]Triazolo[1,5-*a*]pyrid-7-yl) (3,4,5-Trimethoxyphenyl) Methanol (3a). 3a was obtained according to general procedure A′ (0.20 g, 32%) and isolated after purification by flash chromatography on silica gel (AcOEt/cyclohexane 80:20) as a yellow powder. Mp: <50 °C. ^{1}H NMR ($CDCl_3$): δ 3.72 (s, 9H), 6.48 (s, 1H), 6.74 (s, 2H), 6.83 (d, 1H, J = 7.0 Hz), 7.17 (dd, 1H, J = 9.0, 7.0 Hz), 7.58 (d, 1H, J = 9.0 Hz), 7.99 (s, 1H), OH not seen. ^{13}C NMR ($CDCl_3$): δ 153.6 (2C), 140.8 (C), 138.0 (C), 135.0 (C), 134.4 (C), 126.3 (CH), 126.1 (CH), 117.2 (CH), 113.3 (CH), 104.5 (2CH), 71.2 (CH), 61.2 (CH_3), 56.4 ($2CH_3$). IR (KBr) ν: 3274, 3007, 2938, 2839, 1638, 1594, 1506, 1463, 1421, 1327, 1234, 1184, 1127, 1005, 967, 815, 754, 700, 665, and 577 cm^{-1}. HRMS: calcd for $C_{16}H_{17}N_3O_4$ ($M^{+\bullet}$) 315.1219, found 315.1225.

(3-Methyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl) (3,4,5-Trimethoxyphenyl) Methanol (3b). 3b was obtained according to general procedure A′ (0.40 g, 61%) and isolated after purification by flash chromatography on silica gel (AcOEt/cyclohexane 80:20) as a yellow powder. Mp: 144−146 °C. ^{1}H NMR ($CDCl_3$): δ 2.62 (s, 3H), 3.82 (s, 9H), 6.48 (s, 1H), 6.72 (d, 1H, J = 7.0 Hz), 6.80 (s, 2H), 7.17 (dd, 1H, J = 9.0, 6.8 Hz), 7.58 (d, 1H, J = 9.0 Hz), OH not seen. ^{13}C NMR ($CDCl_3$): δ 153.8 (2C), 140.1 (C), 138.3 (C), 135.4 (C), 134.3 (C), 132.5 (C), 124.6 (CH), 117.0 (CH), 113.6 (CH), 104.5 (2CH), 71.9 (CH), 61.3 (CH_3), 56.5 ($2CH_3$), 10.8 (CH_3). IR (KBr) ν: 3468, 2943, 2831, 1639, 1595, 1509, 1450, 1422, 1332, 1224, 1176, 1129, 1076, 1002, 957, 833, 798, 771, 736, 696, 665, 582, 530, and 492 cm^{-1}. HRMS: calcd for $C_{17}H_{19}N_3O_4$ ($M^{+\bullet}$) 329.1376, found 329.1357.

(3-Phenyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl) (3,4,5-Trimethoxyphenyl) Methanol (3c). 3c was obtained according to general procedure A′ (0.40 g, 51%) and isolated after purification by flash chromatography on silica gel (AcOEt/cyclohexane 80:20) as a yellow powder. Mp: <50 °C. ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 9H), 4.95 (s, 1H), 6.48 (s, 1H), 6.75 (s, 2H), 6.79 (d, 1H, J = 6.8 Hz), 7.20 (dd, 1H, J = 8.9, 6.8 Hz), 7.30 (m, 1H), 7.40 (m, 2H), 7.84 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 152.2 (2C), 139.6 (C), 137.3 (C), 135.8 (C), 133.3 (C), 130.1 (C), 129.9 (C), 128.0 (2CH), 127.1 (CH), 125.7 (2CH), 125.1 (CH), 116.2 (CH), 112.2 (CH), 103.1 (2CH), 70.0 (CH), 59.8 (CH_3), 54.9 ($2CH_3$). IR (KBr) ν: 3370, 2937, 2836, 1635, 1593, 1547, 1506, 1462, 1421, 1329, 1233, 1184, 1126, 1075, 1004, 959, 832, 799, 778, 738, 694, 665, and 583 cm^{-1}. HRMS: calcd for $C_{22}H_{21}N_3O_4$ ($M^{+\bullet}$) 391.1532, found 391.1578.

3,7-Diiodo-[1,2,3]triazolo[1,5-*a*]pyridine (5a). 5a was obtained according to general procedure C (0.49 g, 66%) and isolated after purification by flash chromatography on silica gel (heptane/AcOEt 50:50) as a beige powder. Mp: 144 °C. ^{1}H NMR ($CDCl_3$): δ 7.08 (dd, 1H, J = 8.7, 6.8 Hz), 7.53 (d, 1H, J = 5.9 Hz), 7.60 (d, 1H, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 80.9 (C), 86.4 (C), 117.9 (CH), 127.1 (CH), 128.1 (CH), 136.7 (C). Anal. Calcd for $C_6H_3I_2N_3$ (370.92): C, 19.43; H, 0.82; N, 11.33. Found: C, 19.74; H, 0.97; N, 11.18.

3-(5,6-Diiodo-2-pyridyl)-4-iodo-[1,2,3]triazolo[1,5-*a*]pyridine (6′e). 6′e was obtained according to general procedure C (0.34 g, 30%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 95:5) as a white powder. Mp: 245 °C. ^{1}H NMR [$(CD_3)_2SO$]: δ 7.03 (t, 1H, J = 7.0 Hz), 7.76 (d, 1H, J = 8.2 Hz), 8.00 (dd, 1H, J = 7.0, 0.65 Hz), 8.11 (d, 1H, J = 8.2 Hz), 9.23 (dd, 1H, J = 7.0, 0.65 Hz). ^{13}C NMR [$(CD_3)_2SO$]: δ 82.0 (C), 101.7 (C), 118.8 (C), 117.2 (CH), 125.9 (CH), 131.9 (C), 136.3 (CH), 137.3 (CH), 139.5 (C), 147.6 (CH), 154.5 (C). Anal. Calcd for $C_{11}H_5I_3N_4$ (573.90): C, 23.02; H, 0.88; N, 9.76. Found: C, 23.31; H, 1.11; N, 9.86.

7-Iodo-3-(5-iodo-2-thienyl)-[1,2,3]triazolo[1,5-*a*]pyridine (5f). 5f was obtained according to general procedure C (0.68 g, 75%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2) as a yellow powder. Mp: 201 °C. ^{1}H NMR ($CDCl_3$): δ 7.09 (dd, 1H, J = 9.0, 6.8 Hz), 7.22−7.32 (m, 2H), 7.53 (dd, 1H, J = 6.9, 0.9 Hz), 7.92 (dd, 1H, J = 9.0, 1.0 Hz). ^{1}H NMR [$(CD_3)_2SO$]: δ 7.25 (t, 1H, J = 7.9 Hz), 7.36−7.41 (m, 2H), 7.75 (d, 1H, J = 6.9 Hz), 8.21 (d, 1H, J = 8.8 Hz). ^{13}C NMR [$(CD_3)_2SO$]: δ 76.1 (C), 90.0 (C), 117.7 (CH), 125.8 (CH), 127.8 (CH), 127.9 (CH), 129.5 (C), 133.4 (C), 137.9 (CH), 138.8 (C). Anal. Calcd for $C_{10}H_5I_2N_3S$ (453.04): C, 26.51; H, 1.11; N, 9.28; S, 7.08. Found: C, 26.77; H, 1.17; N, 9.27; S, 7.27.

7-(2-Pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine (4a). 4a was obtained according to general procedure D (67 mg, 17%) or E (0.10 g, 26%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 80:20) as a white powder. Mp: 94 °C. ^{1}H NMR ($CDCl_3$): δ 7.39−7.45 (m, 2H), 7.82 (dd, 1H, J = 8.7, 1.0 Hz), 7.90−7.96 (m, 2H), 8.21 (s, 1H), 8.79−8.80 (m, 1H), 9.00 (d, 1H, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$): δ 116.7 (CH), 118.0 (CH), 124.5 (CH), 125.3 (CH), 125.7 (CH), 126.2 (CH), 135.1 (C), 136.7 (C), 136.9 (CH), 149.2 (C), 149.9 (CH). IR (KBr) ν: 3134, 3059, 2926, 2862, 1634, 1584, 1570, 1510, 1466, 1436, 1417, 1369, 1324, 1262, 1206, 1153, 1102, 1046, 995, 976, 953, 902, 837, 769, 732, 698, 678, 627, 612, 576, and 496 cm^{-1}. HRMS: calcd for $C_{11}H_8N_4$ ($M^{+\bullet}$) 196.0749, found 196.0732. Anal. Calcd for $C_{11}H_8N_4$ (196.21): C, 67.34; H, 4.11; N, 28.55. Found: C, 67.06; H, 4.29; N, 28.29.

3-Methyl-7-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine (4b). 4b was obtained according to general procedure D (0.10 g, 24%) or E′ (0.16 g, 38%) and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/AcOEt 80:20) as a white powder. Mp: 68 °C. ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 3H), 7.32 (m, 2H), 7.70 (dd, 1H, J = 8.7, 1.0 Hz), 7.89−7.95 (m, 2H), 8.78 (d, 1H, J = 4.5 Hz), 9.02 (d, 1H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 10.6 (CH_3), 116.6 (CH), 117.6 (CH), 124.2 (CH), 124.4 (CH), 125.2 (CH), 133.1 (C), 134.8 (C), 136.5 (C), 136.9 (CH), 149.4 (C), 149.8 (CH). IR (KBr) ν: 3053, 3010, 2926, 2852, 1630, 1583, 1533, 1467, 1429, 1380, 1343, 1315, 1203, 1155, 1125, 1089, 1045, 990, 947, 808, 777, 731, 696, 676, 616, and 568 cm^{-1}. HRMS: calcd for $C_{12}H_{10}N_4$ ($M^{+\bullet}$) 210.0905, found 210.0869. Anal. Calcd for $C_{12}H_{10}N_4$ (210.23): C, 68.56; H, 4.79; N, 26.65. Found: C, 68.31; H, 4.78; N, 26.53.

3-Phenyl-7-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine (4c). 4c was obtained according to general procedure D (0.33 g, 60%) or E (0.36 g, 67%) and isolated after purification by flash chromatography on silica gel (heptane/AcOEt 50:50) and recrystallization from heptane/Et_2O (30:70) as a yellow powder. Mp: 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 7.39−7.57 (m, 5H), 7.91−8.02 (m, 4H), 8.09 (dd, 1H,

J = 8.9, 1.0 Hz), 8.80 (ddd, J = 3.8, 1.6, 0.8 Hz), 9.05 (d, 1H, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 117.0 (CH), 118.4 (CH), 124.5 (CH), 125.4 (CH), 126.1 (CH), 127.0 (2CH), 128.1 (CH), 129.1 (2CH), 131.6 (C), 131.9 (C), 136.8 (CH), 137.0 (C), 138.3 (C), 149.2 (C), 149.9 (CH). IR (KBr) ν: 3064, 2989, 1630, 1605, 1571, 1532, 1496, 1466, 1427, 1349, 1318, 1299, 1265, 1220, 1159, 1139, 1117, 1072, 1051, 1008, 990, 916, 802, 782, 748, 736, 696, 616, 599, and 564 cm^{-1}. HRMS: calcd for $C_{17}H_{12}N_4$ ($M^{+\bullet}$) 272.1062, found 272.1026. Anal. Calcd for $C_{17}H_{12}N_4$ (272.30): C, 74.98; H, 4.44; N, 20.58. Found: C, 74.71; H, 4.39; N, 20.33.

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Supporting Information Available: General procedures, X-ray diffraction analysis of compounds **2a**, **2d**, and **2′e**, and copies of ^{1}H and ^{13}C NMR spectra for compounds **2a**−**d**, **2′e**, **2f**, **3a**−**c**, **4a**−**c**, **5a**, **5f**, and **6′e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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