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VOLUME 7
NUMBER 1

ChemFiles

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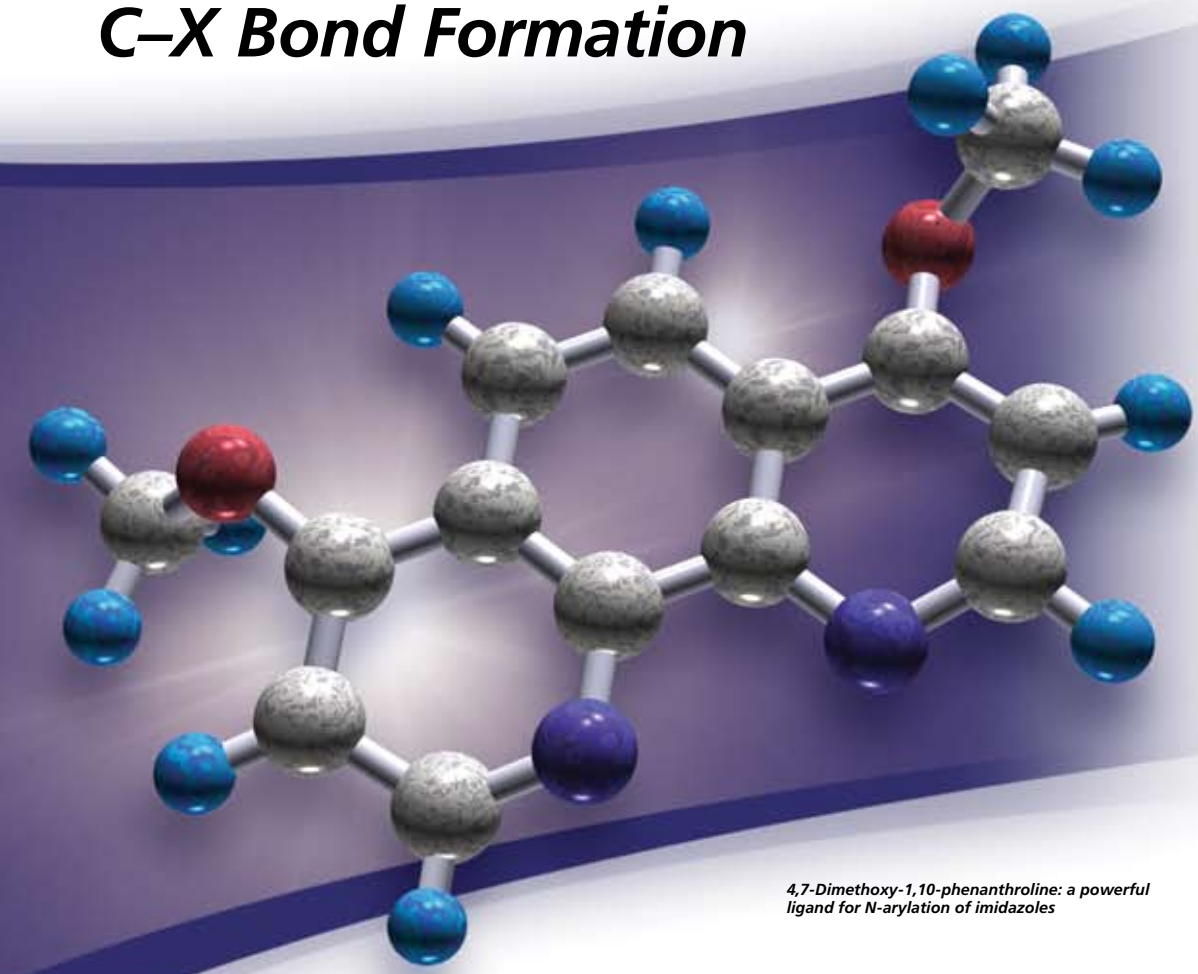
C–X Bond Formation



4,7-Dimethoxy-1,10-phenanthroline: a powerful ligand for N-arylation of imidazoles

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Introduction

This edition of *ChemFiles* describes the applications of new reagents, catalysts, and ligands used in the formation of a C–X bond. While a variety of reaction paradigms are discussed, there is a common theme—the tools necessary to effect these reactions have all been applied in the hottest areas of synthetic organic chemistry and they exhibit superb levels of chemo-, regio-, and stereoselectivity. Topics such as click chemistry, C–H activation, and C–N coupling reactions have become increasingly prevalent over the past decade and new tools to execute these powerful reactions are always needed, particularly in the area of drug discovery. Sigma-Aldrich™ is proud to provide cutting-edge products for the rapid and successful construction of complex chemical architectures. For a complete listing of products related to chemical synthesis, please visit us at **sigma-aldrich.com/chemicalsynthesis**.

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About Our Cover

The cover graphic depicts the structure of 4,7-dimethoxy-1,10-phenanthroline, a ligand that has been successfully employed by the Buchwald group at MIT in Cu-catalyzed *N*-arylation of imidazoles. Arylated imidazoles appear in numerous pharmacologically active molecules, and are difficult to prepare.

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Click Chemistry

Perhaps no reaction in the click family has received more attention than the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes with organoazides to yield 1,4-disubstituted 1,2,3-triazoles (**Scheme 1**).[1] True to a "good" click reaction, the reaction is reliable and high yielding, easy to perform, invariant to the presence of air or moisture, and tolerant of a wide range of functional groups. In many instances, water is the ideal reaction solvent, providing the best yields and highest rates. Typically, the cycloadducts are solids, obviating the need for chromatographic purification. The 1,2,3-triazole ring is resistant to hydrolysis, oxidation, reduction, or other modes of cleavage. All of these properties make the Cu(I)-catalyzed azide-alkyne cyclization an important weapon in library development during the drug discovery process.[2]

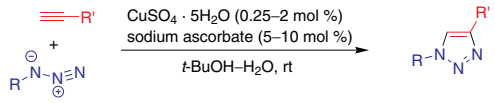
The use of a Cu(II) salt in the presence of an ascorbate reducing agent to form catalytically-active Cu(I) has been the method of choice for the preparative synthesis of 1,2,3-triazoles, but can be problematic in bioconjugation applications. A Cu(I) salt such as $[Cu(CH_3CN)_4]PF_6$ may be used directly in the presence of the stabilizing ligand tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, TBTA (**Figure 1**).[3] TBTA has been shown to effectively enhance the copper-catalyzed cycloaddition without damaging biological scaffolds.

Whereas the Cu(I)-catalyzed reaction provides access to 1,4-disubstituted triazoles, a transition metal variant allows for access to the complementary 1,5-isomer. Treatment of a terminal or internal alkyne with an azide in the presence of catalytic $Cp^*RuCl(PPh_3)_2$ cleanly provides the cycloadduct in superb yield with complete control of regiospecificity (**Scheme 2**).[4]

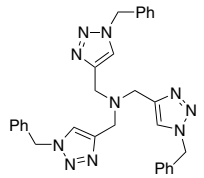
Of course, many organoazides are not commercially available. Carreira and co-workers recently reported the Co(II)-catalyzed hydroazidation of unactivated olefins with *p*-toluenesulfonyl azide (TsN_3) to yield alkyl azides (**Scheme 3**).[5] The catalyst is easily prepared in situ from $Co(BF_4)_2 \cdot 6H_2O$ and a Schiff base ligand. Mono-, di-, and trisubstituted olefins are tolerated in the hydroazidation reaction and complete Markovnikov selectivity is observed. Additionally, the reaction can be coupled to the Sharpless triazole cycloaddition to give the 1,4-triazole in a one-pot process.

Sigma-Aldrich is pleased to offer a variety of reagents, catalysts, and ligands for your research needs in the exciting field of click chemistry.

References: (1) (a) Rostovtsev, V. V. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W. et al. *J. Org. Chem.* **2002**, *67*, 3057. (c) Kolb, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (d) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today*, **2003**, *8*, 1128. (2) (a) Manetsch, R. et al. *J. Am. Chem. Soc.* **2004**, *126*, 12809. (b) Lewis, W. G. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053. (c) Speers, A. E. et al. *J. Am. Chem. Soc.* **2003**, *125*, 4686. (3) Chan, T. R. et al. *Org. Lett.* **2004**, *6*, 2853. (4) Zhang, L. et al. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (5) (a) Waser, J. et al. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (b) Waser, J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (c) *p*-Toluenesulfonyl azide, TsN_3, can be readily prepared from TsCl and sodium azide: Regitz, M. et al. *Organic Syntheses* **1973**, *Coll. Vol. 5*, 179.

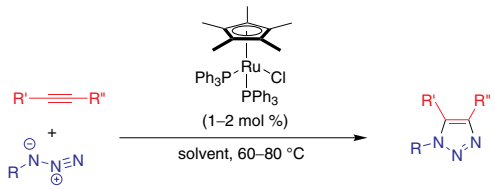


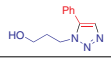
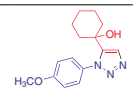
Scheme 1



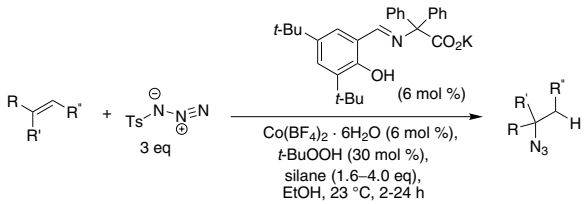
TBTA

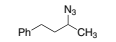
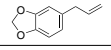
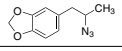
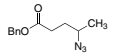
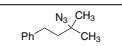
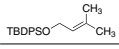
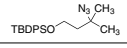
Figure 1



Entry	Product	Solvent	Time (h)	Yield (%)
1		C_6H_6	2	80
2		C_6H_6	2.5	94
3		dioxane	2	82
4		dioxane	12	94
5		C_6H_6	2	~100

Scheme 2



Entry	Alkene	Product	Silane	Yield (%)
1			$PhSiH_3$	90
2			$PhSiH_3$	65
3			tetramethyl-disiloxane (TMDSO)	77
4			TMDSO	90
5			$PhSiH_3$	63

Scheme 3

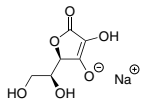
Copper(II) sulfate pentahydrate, ≥98.0%

$CuSO_4 \cdot 5H_2O$
FW: 249.69
[*7758-99-8*]

209198-5G	5 g
209198-100G	100 g
209198-250G	250 g

(+)-Sodium L-ascorbate, ≥98%

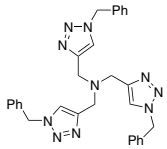
$C_6H_7NaO_6$
FW: 198.11
[*134-03-2*]



A7631-25G	25 g
A7631-100G	100 g
A7631-500G	500 g

Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, 97% NEW

TBTA
$C_{30}H_{30}N_{10}$
FW: 530.63



678937-50MG	50 mg
678937-500MG	500 mg

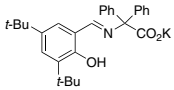
Pentamethylcyclopentadienylbis-(triphenylphosphine)ruthenium(II) chloride NEW

$C_{46}H_{45}ClP_2Ru$
FW: 796.32
[*92361-49-4*]

673293-250MG	250 mg
673293-1G	1 g

Potassium 2-(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-2,2-diphenylacetate, 95% NEW

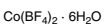
$C_{29}H_{32}KNO_3$
FW: 481.67



676551-250MG	250 mg
676551-1G	1 g

Cobalt(II) tetrafluoroborate hexahydrate, 99%

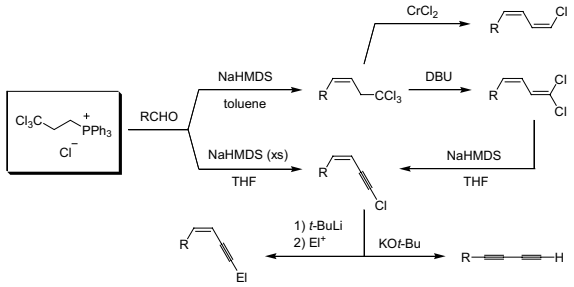
$Co(BF_4)_2 \cdot 6H_2O$
FW: 340.63
[*15684-35-2*]



399957-25G	25 g
399957-100G	100 g

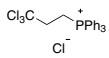
Dienes, Enynes, and Diynes Made Easy

Conjugated π-systems are prevalent in a variety of natural products and have often been prepared through transition metal-mediated cross-couplings. Professor Philip Fuchs of Purdue University recently reported an alternative approach relying on a Wittig-type reagent possessing a latent acetylene moiety. Treatment of an aldehyde with the ylide derived from 3,3,3-trichloropropyl-1-triphenylphosphonium chloride allows for easy access to (*Z*)-1,3-enynes, (*Z*,*Z*)-1-chloro-1,3-dienes, and 1,3-diynes. In 2006, this reagent was successfully employed to construct the bis(enyne) segments of the alkaloid natural product histrionicotoxin (HTX).[1]



3,3,3-Trichloropropyl-1-triphenylphosphonium chloride, 95% NEW

$C_{21}H_{19}Cl_4P$
FW: 444.16



675121-1G	1 g
675121-5G	5 g

References: (1) (a) Karatholuvhu, M. S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 14314. (b) Karatholuvhu, M. S. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12656.

Tools for C–H Amination

The Du Bois group at Stanford University has made substantial progress within the field of Rh-catalyzed C–H amination via oxidative cyclization of carbamate, sulfamate, sulfamide, urea, and guanidine substrates to give 1,2- and 1,3-heteroatom motifs masked in the form of 5- and 6-membered ring heterocycles (**Scheme 1**).[1,2] The cyclization can occur with a high degree of stereospecificity for optically active substrates.

Additionally, heterocyclic urea and guanidines themselves appear as structural elements in pharmacologically interesting substrates such as NK_1 receptor antagonists, toxins, and bromopyrrole metabolites (**Figure 1**).[2b,2g]

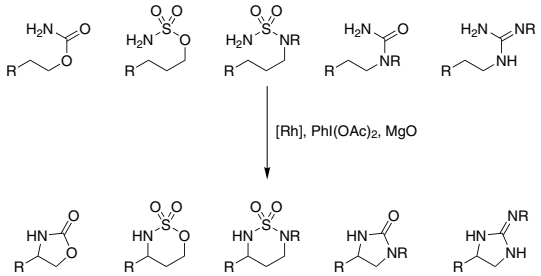
A variety of Rh-carboxylate catalysts exhibit at least some effectiveness in the urea and guanidine cyclizations, but the most promising results are obtained using the combination of catalytic $Rh_2(esp)_2$ with substrates bearing 2,2,2-trichloroethoxysulfonyl (Tces) protection at nitrogen. Installation of the urea or guanidine residue, followed by cyclization can be accomplished through the use of several reagents as outlined in Schemes 2–6.[2b] Mitsunobu reaction of an alcohol with Tces-protected urea gives the cyclization precursor in good yield (**Scheme 2**). Subsequent treatment of this species with $Rh_2(esp)_2$ in the presence of $PhI(OAc)_2$ and MgO affords the cyclized product in good to excellent yields for substrates containing tertiary or benzylic β-C–H centers (**Scheme 3**).

Tces-protected guanidines are easily prepared by of the reaction of an amine with one of two reagents derived from *S,S*-dimethyl-*N*-(2,2,2-trichloroethoxysulfonyl)carbonimidodithionate (**Scheme 4**).

The isothiourea reacts with most primary amines in water at 100 °C to give the Tces-protected guanidine derivative (**Scheme 5**). Alternatively, more functionalized amines can be reacted with the carbonchloroimidodithioate reagent to give an intermediate pseudothiourea that can be transformed into the desired guanidine using HMDS as an ammonia source.

Treatment of these Tces-protected guanidines under the standard oxidative cyclization reaction conditions furnishes the cyclized products in good yield (**Scheme 6**). Like the urea cyclizations, the reaction is most successful for substrates containing tertiary or benzylic β-C–H centers. Removal of the protecting group can be effected in high-yield using Zn metal and methanolic acetic acid.

References: (1) *ChemFiles* Vol. 5 No. 10. (2)(a) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926. (b) Kim, M. et al. *Org. Lett.* **2006**, *8*, 1073. (c) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685. (d) Espino, C. G. et al. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (e) Fiori, K. W. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349. (f) When, P. M. et al. *Org. Lett.* **2003**, *5*, 4823. (g) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.



Scheme 1

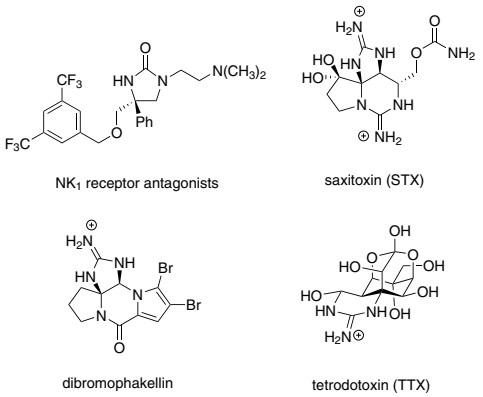
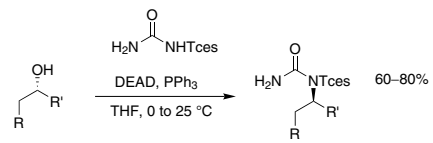
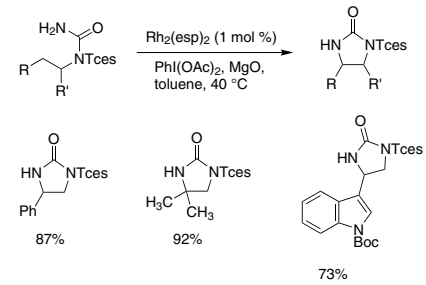


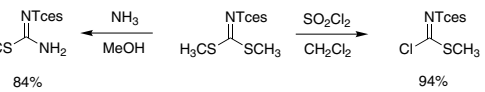
Figure 1



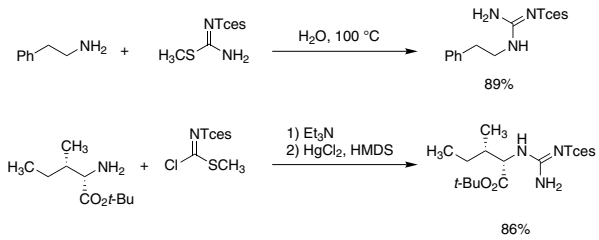
Scheme 2



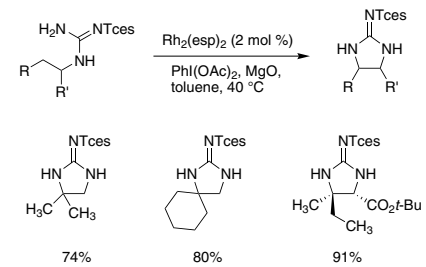
Scheme 3



Scheme 4



Scheme 5

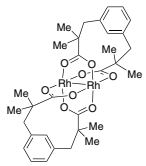


Scheme 6

Bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], 96%

NEW

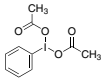
$Rh_2(esp)_2$
$C_{32}H_{40}O_8Rh_2$
FW: 758.47
[*819050-89-0*]



662623-100MG	100 mg
662623-500MG	500 mg

(Diacetoxyiodo)benzene, 98%

$C_{10}H_{11}IO_4$
FW: 322.1
[*3240-34-4*]

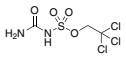


178721-5G	5 g
178721-25G	25 g
178721-100G	100 g

N-(2,2,2-Trichloroethoxysulfonyl)urea

NEW

Tces-urea
$C_3H_5Cl_3N_2O_4S$
FW: 271.51

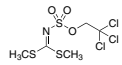


680834-1G	1 g
680834-5G	5 g

S,S-Dimethyl *N*-(2,2,2-trichloroethoxysulfonyl)-carbonimidodithionate

NEW

$C_5H_8Cl_3NO_3S_3$
FW: 332.68

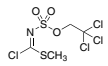


679879-1G	1 g
679879-5G	5 g

S-Methyl *N*-(2,2,2-trichloroethoxysulfonyl)-carbonchloroimidothioate

NEW

$C_4H_5Cl_4NO_3S_2$
FW: 321.03

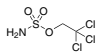


679712-1G	1 g
679712-5G	5 g

2,2,2-Trichloroethoxysulfonamide, 97%

NEW

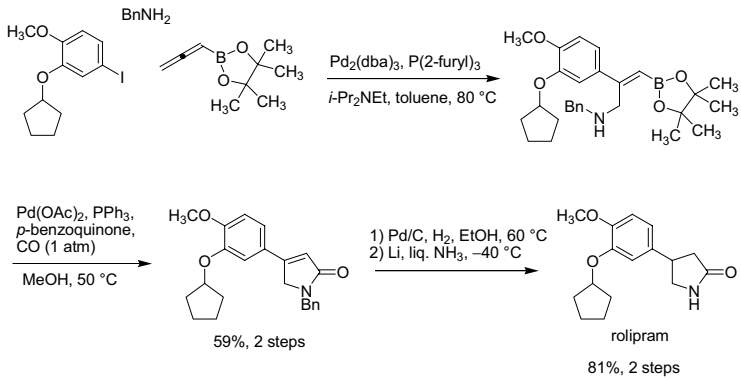
Tces-NH_2
$C_2H_4Cl_3NO_3S$
FW: 228.48
[*69226-51-3*]



663727-1G	1 g
663727-10G	10 g

Allenylboronic Acid Pinacol Ester

The allenylboronate platform has recently been demonstrated to undergo multi-component reactions in a completely regio- and stereoselective fashion.[1] Yoshida and co-workers successfully utilized this three-carbon building block in a concise synthesis of rolipram, which is a selective inhibitor of phosphodiesterase-4 (PDE-4), an anti-inflammatory agent and antidepressant.[1b] In the course of the four-component reaction both a C–C and C–N bond are formed, presumably through a Pd-allyl intermediate.

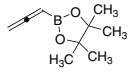


References: (1) (a) Tonogaki, K. et al. *Org. Lett.* **2006**, *8*, 1419. (b) Tonogaki, K. et al. *J. Am. Chem. Soc.* **2006**, *128*, 1464. (c) Bustelo, E. et al. *J. Am. Chem. Soc.* **2005**, *127*, 11582.

Allenylboronic acid pinacol ester, 97%

NEW

$C_9H_{15}BO_2$
FW: 166.03
[*865350-17-0*]



678554-1G	1 g
678554-5G	5 g

Ketone and Aldehyde α-Oxygenation

The α-hydroxycarbonyl moiety is an important structural motif in organic synthesis and is present in a substantial number of natural products. A variety of methods have been developed to prepare this functionality including α-oxygenation of enolates with electrophilic oxidizing agents, as well as dihydroxylation or epoxidation of enol ethers.[1] Recently, aminooxylation of aldehydes[2] and ketones[3] has been demonstrated using nitrosobenzene. However, this latter protocol requires a large excess of the carbonyl compound in tandem with syringe pump techniques that diminishes the usefulness of the transformation.

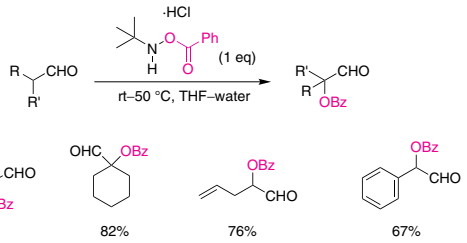
Nicholas Tomkinson of Cardiff University (UK) recently reported several practical reagents for the preparation of α-oxygenated carbonyl compounds.[4] *N-tert*-butyl-*O*-benzoylhydroxylamine hydrochloride is a bench stable reagent for the α-functionalization of a variety of aldehydes under mild conditions (**Scheme 1**). The reaction can be performed in open air and in the presence of moisture. Benzoylation occurs in high-yield at both secondary and tertiary centers as demonstrated by the reactions of this reagent with isovaleraldehyde and cyclohexanecarboxaldehyde.

While this reagent is only useful on aldehyde substrates, a similar bench stable reagent can be applied towards the α-oxygenation of ketones. Treatment of cyclohexanone with *N*-methyl-*O*-benzoylhydroxylamine hydrochloride in water provides the benzoyl-protected alcohol in excellent yield, presumably through a pericyclic rearrangement of an intermediate iminium ion (**Scheme 2**). A previous synthesis of this molecule by House required a laborious five-step procedure.[5]

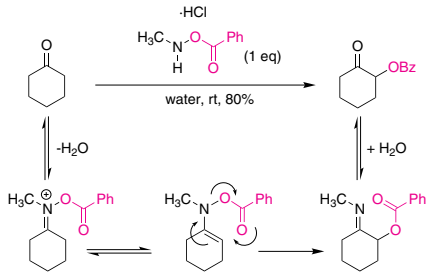
Both acyclic and cyclic ketones undergo oxidation at mild temperatures to afford protected alcohols in good to excellent yield (**Scheme 3**). The reagent is tolerant of existing functionality (e.g. sulfonamides, free hydroxyl groups, and unsaturation), and in the case of unsymmetrical ketones, oxidation occurs regiospecifically at the more substituted carbon. In addition to water and DMSO, THF and $CHCl_3$ can be used as solvents with similar yields.

Sigma-Aldrich is delighted to add these new tools to our ever-growing arsenal of oxidation reagents.

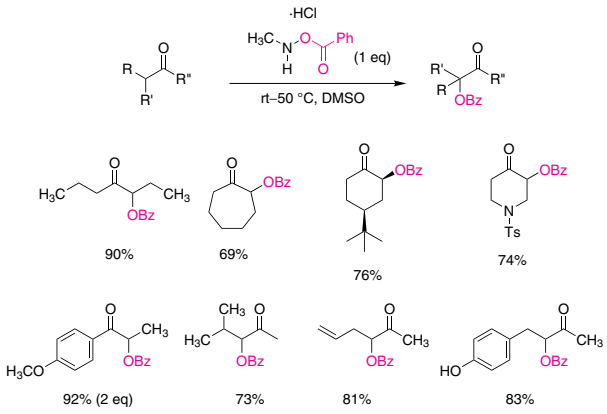
References: (1) Chen, B.-C. et al. *Org. React.* **2003**, *62*, 1. (2) (a) Brown, S. P. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y. et al. *Tetrahedron Lett.* **2003**, *44*, 8293. (3) (a) Bøgevig, A. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317. (b) Hayashi, Y. et al. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (c) Córdova, A. et al. *Chem. Eur. J.* **2004**, *10*, 3673. (4) (a) Beshara, C. S. et al. *Chem. Commun.* **2005**, 1478. (b) Beshara, C. S. et al. *Org. Lett.* **2005**, *7*, 5729. (5) House, H. O.; Richey, F. A. *J. Org. Chem.* **1969**, *34*, 1430.



Scheme 1



Scheme 2

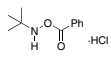


Scheme 3

N-tert-Butyl-*O*-benzoylhydroxylamine hydrochloride, 97%

NEW

$C_{11}H_{16}ClNO_2$
FW: 229.70

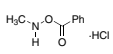


669407-1G	1 g
669407-5G	5 g

N-Methyl-*O*-benzoylhydroxylamine hydrochloride, 97%

NEW

$C_8H_{10}ClNO_2$
FW: 187.62



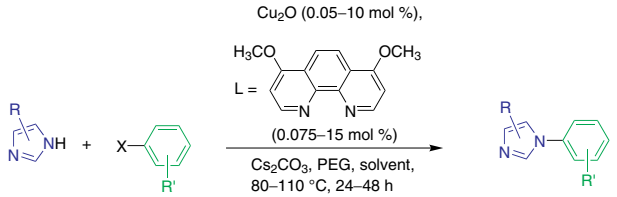
669393-1G	1 g
669393-5G	5 g

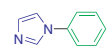
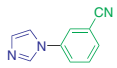
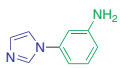
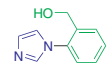
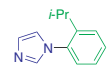
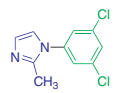
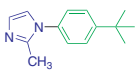
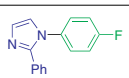
Buchwald Ligands for C–N Coupling

Although many methodologies have been developed for C–N coupling reactions, until recently there were no general methods available for the *N*-arylation of imidazoles. Traditional methods for arylation included nucleophilic aromatic substitution of an activated aryl halide or by copper-mediated coupling of the imidazole with an aryl iodiole (Ullmann coupling). The former approach was limited in scope because it required an aryl halide bearing strongly electron-withdrawing substituents, while the latter protocol necessitated harsh reaction conditions and stoichiometric copper. The Buchwald group at MIT has developed a mild and high-yielding approach to arylated imidazoles using catalytic Cu(I) and a 1,10-phenanthroline ligand scaffold.[1] Both aryl bromides and iodides are effective electrophiles, and the reaction conditions tolerate bulky substituents on either coupling partner. Additionally, the reaction is functional group tolerant, with cyano, nitro, ester, amino, hydroxyl, and halogen groups remaining intact during the course of the reaction (**Scheme 1**).

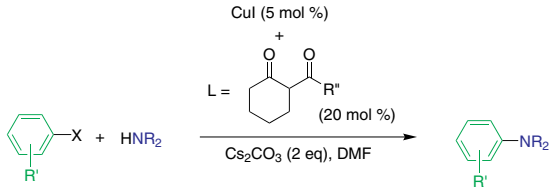
The Buchwald group has also made significant advances in the area of mild Ullmann-type couplings of aryl halides with primary and secondary amines in the presence of CuI and a β-diketone ligand (**Scheme 2**).[2] Heterocyclic structures may be present in either coupling partner, and a variety of functional groups are tolerated in the reaction conditions (e.g. carboxylic acids, Boc protecting groups, ketones, and olefins). Moreover, reactions of aryl iodides can typically be performed at ambient temperatures.

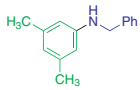
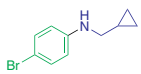
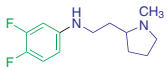
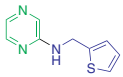
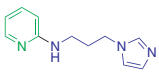
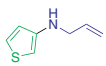
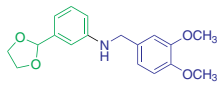
References: (1) (a) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779. (b) Kiyomori, A. et al. *Tetrahedron Lett.* **1999**, *40*, 2657. (2) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.



Entry	Product	X	Cu/L (mol %)	Solvent	Yield (%)
1		I	0.05/0.075	*n*-PrCN	95
2		I	5/7.5	CH_3CN	95
3		Br	10/15	*n*-PrCN	92
4		I	5/7.5	*n*-PrCN	94
5		I	5/7.5	*n*-PrCN	94
6		I	5/7.5	*n*-PrCN	84
7		Br	10/15	*n*-PrCN	95
8		I	5/7.5	*n*-PrCN	85

Scheme 1

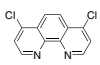


Entry	Product	X	R"	Yield (%)
1		I	CH_3	94
			i-Pr	96
2		I	CH_3	96
			i-Pr	98
3		I	CH_3	98
			i-Pr	98
4		I	*i*-Pr	99
5		I	*i*-Pr	90
6		I	*i*-Pr	83
7		Br	*i*-Pr	89

Scheme 2

4,7-Dichloro-1,10-phenanthroline NEW

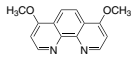
$C_{12}H_6Cl_2N_2$
FW: 249.10



678015-250MG	250 mg
678015-1G	1 g

4,7-Dimethoxy-1,10-phenanthroline NEW

$C_{14}H_{12}N_2O_2$
FW: 240.26
[*92149-07-0*]



678023-250MG	250 mg
678023-1G	1 g

2-Acetylcyclohexanone, 97%

$C_8H_{12}O_2$
FW: 140.18
[*874-23-7*]

179760-5G	5 g
179760-25G	25 g

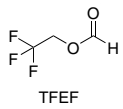
Heteroatom Formylation

Formate esters and formamides are valuable synthetic intermediates, and a variety of synthetic protocols have been devised for formylation of heteroatoms including the use of in situ-generated formic anhydride,[1] mixed formic anhydrides,[2] or activated formate esters.[3] Anhydride methodologies can often be unreliable, and if the molecule contains both hydroxyl group and amine functionalities, the reaction is often unselective, giving both *O*- and *N*-formyl adducts. Protocols using activated formate esters (or cyanomethylformate[4]) are often *O*-selective, thus precluding their use if protection at nitrogen is desired for an amino alcohol or hydroxylamine substrate.

Recently, 2,2,2-trifluoroethyl formate (TFEF, **Figure 1**) was shown to be a competent reagent for formylation at carbon, nitrogen, and oxygen atoms. As shown in **Scheme 1**, amines, alcohols, and *N*-hydroxylamines readily undergo reaction with TFEF in high yield.[5] For optically active substrates, no loss of enantiopurity is observed. The reaction is also chemoselective as well, with *N*-formylation being the predominant reaction pathway for amino alcohols and hydroxylamines, provided that either formic acid or sodium formate is added to the reaction mixture. The reaction conditions are generally mild (typically between 0 and 65 °C), and common solvents are employed (MTBE, THF).

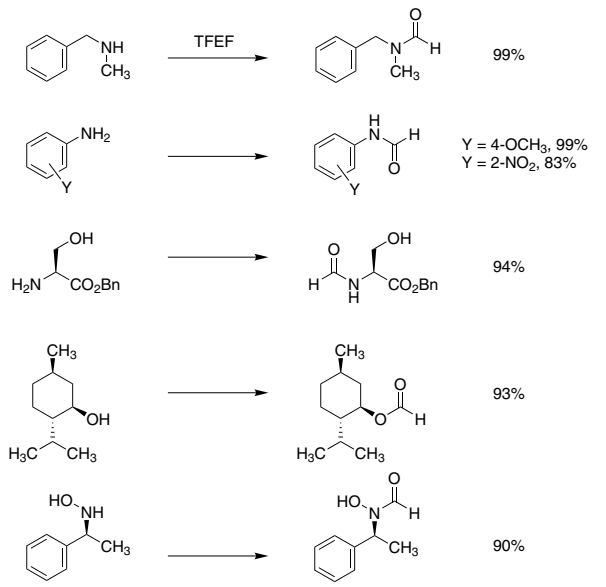
Lastly, TFEF is also a useful reagent for the preparation of α-formyl ketones via *C*-formylation of kinetically-generated ketone enolates (**Scheme 2**). Hydroxymethylene ketones are critically important synthetic intermediates, and typically the classic Claisen formylation reaction (base-induced condensation of a ketone and a formate ester) was the only general method for their preparation. Unfortunately, the scope of the classical method is severely limited because of the equilibrating conditions required for reaction success. TFEF reacts rapidly with pre-formed ketone enolates to give the α-formylated product in good to excellent yields, often in a complementary fashion to the classical variant (**Scheme 3**).

References: (1) (a) Chen, F. M. F.; Benoiton, N. L. *Synthesis* **1979**, 709. (b) Waki, M.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 2019. (c) Strazzolini, P. et al. *Tetrahedron* **1990**, *46*, 1081. (2) (a) Kisfaludy, L.; Otvos, L., Jr. *Synthesis* **1987**, 510. (b) Yamamoto, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1253. (c) Martinez, J.; Laur, J. *Synthesis* **1982**, 979. (d) Yale, H. L. *J. Org. Chem.* **1971**, *36*, 3238. (e) Kitagawa, T. et al. *Chem. Pharm. Bull.* **1994**, *42*, 1931. (3) (a) Deutch, J.; Niclas, H.-J. *Synth. Commun.* **1993**, *23*, 1561. (b) Duczek, W. et al. *Synthesis* **1996**, 37. (4) Hill, D. R. et al. *Org. Lett.* **2002**, *4*, 111. (5) Zayia, G. H. *Org. Lett.* **1999**, *1*, 989.

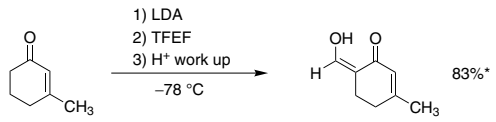


TFEF

Figure 1

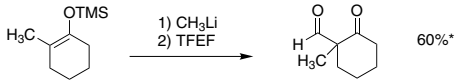


Scheme 1



*Classical method provides this compound in ~35% yield.

Scheme 2

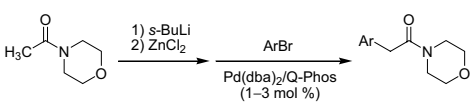


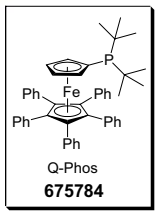
* Classical method using 2-methylcyclohexanone provides the alternative regioisomer. Yield includes $LiAlH_4$ reduction of the crude to give the resulant diols.

Scheme 3

2,2,2-Trifluoroethyl formate, 95% NEW	
TFEF $C_3H_3F_3O_2$ FW: 128.05 [*32042-38-9*]	
669083-1G	1 g
669083-5G	5 g

Q-Phos: A Hindered Ferrocenyl(dialkyl)phosphine Ligand





Q-Phos
675784

Developed by the Hartwig group, Q-Phos is a sterically hindered ferrocenylphosphine ligand that has found broad applicability in a variety of Pd-catalyzed C–C, C–N, and C–O bond-forming reactions including: amination and etherification of aryl chlorides, Suzuki coupling and, most recently, the α-arylation of zinc amide enolates.[1]

References: (1) (a) Hama, T. et al. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Kataoka, N. et al. *J. Org. Chem.* **2002**, *67*, 5553.

Mild Mg–Halogen Exchange

In recent years, substantial progress has been made in magnesium–halogen exchange reactions used for the preparation of functionalized Grignard reagents containing sensitive moieties such as ester or cyano groups.[1] Typically, the exchange must be performed below room temperature to minimize side reactions, and additives are often used to deactivate the Grignard such that the sensitive functional groups can survive the exchange reaction.

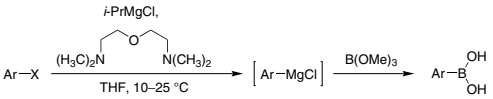
The combination of *i*-PrMgCl and the tridentate ligand bis[2-(*N*,*N*-dimethylamino)ethyl] ether has proven to be an excellent reagent system for non-cryogenic Grignard formation from aryl bromides and iodides bearing sensitive functional groups.[2] Subsequent reaction with an electrophile such as trimethylborate provides a useful method for the preparation of arylboronic acids used in Suzuki coupling (**Scheme 1**). In the presence of the tridentate ligand, both the metal–halogen exchange and the reaction with the electrophile can be performed at 10 to 25 °C. The yields of the newly formed Grignard and the final product are substantially improved in comparison to the identical reaction without a ligand additive.

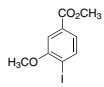
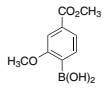
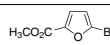
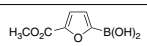
This methodology has also proven to be useful for iodoaromatics bearing a reactive pyrimidine ring (**Scheme 2**).[3] In the absence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether, the magnesium–halogen exchange is plagued with side reactions, including reduction of, and/or nucleophilic addition to the electron-deficient pyrimidine ring by the isopropyl Grignard reagent.

Finally, the ligand also allows for the clean and direct addition of Grignard reagents to aryl acid chlorides to give the corresponding aryl ketones, free from copious amounts of unwanted side products typically observed in the reaction (**Scheme 3**).[4] In the absence of the amino ether ligand, the side products arise from β-elimination of the intermediate Grignard/acid chloride adduct to yield reduction products that detract from the overall yield. The Grignard can be effectively deactivated in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether to afford the desired aryl ketone in substantially better yield.

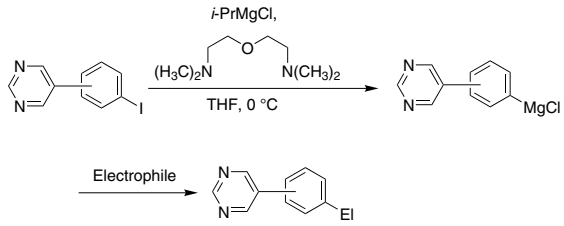
Using this methodology, a diverse set of aryl ketones were prepared in high yield from the corresponding aryl acid chlorides (**Figure 1**). These examples also illustrate the excellent functional group tolerance observed under the reactions conditions.

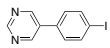
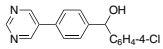
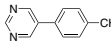
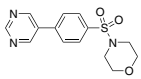
References: (1) For a review, see Knochel, P. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (2) Wang, X.-j. et al. *Org. Lett.* **2006**, *8*, 305. (3) Wang, X.-j. et al. *Org. Lett.* **2006**, *8*, 3141. (4) Wang, X.-j. et al. *Org. Lett.* **2005**, *7*, 5593.



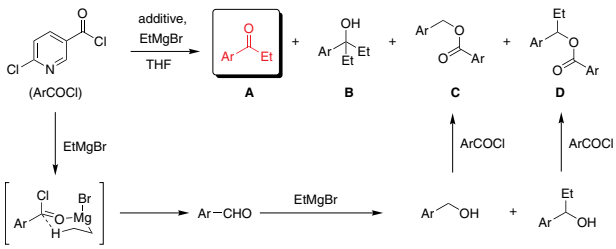
Entry	Aryl halide	Boronic acid	Yield (%)	Yield with no ligand (%)
1			86	28
2			77	28
3			85	82
4			76	69
5			70	–

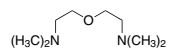
Scheme 1



Entry	Aryl iodide	Electrophile	Product	Yield (%)	Yield with no ligand (%)
1		4-ClC$_6$H$_4$CHO		89	53
2		DMF		81	46
3		SO_2, followed by NCS oxidation and morpholine coupling		95	49

Scheme 2



Entry	Additive	Yield (%) A	B	C	D
1	None	40	3	13	15
2		91	–	–	–

Scheme 3

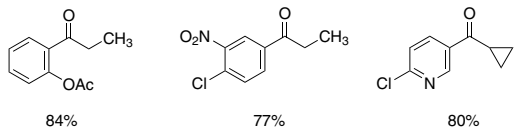
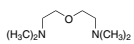


Figure 1

Bis[2-(*N*,*N*-dimethylamino)ethyl] ether, 97%

NEW

BDAEE
$C_8H_{20}N_2O$
FW: 160.26
[*3033-62-3*]



667609-100ML	100 mL
667609-500ML	500 mL

Isopropylmagnesium chloride, 2.0 M in tetrahydrofuran

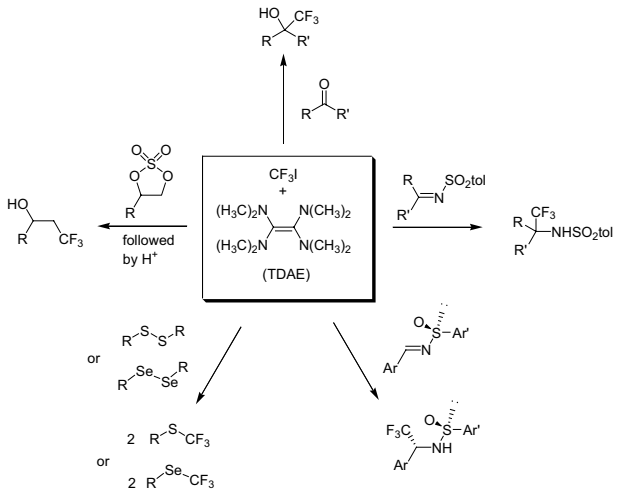
C_3H_7MgCl
FW: 102.85
[*1068-55-9*]

230111-100ML	100 mL
230111-800ML	800 mL

Reagents for Fluorination

Nucleophilic Trifluoromethylation

The trifluoromethyl substituent has long been recognized for the positive influence it can have on the biological activity of molecules. Professor William Dolbier, Jr. (University of Florida) has developed numerous trifluoromethylation reactions using CF_3I in the presence of a powerful two-electron reductant, tetrakis(dimethylamino)ethylene (TDAE), to generate a nucleophilic trifluoromethyl anion. In many cases, the CF_3I/TDAE reagent system is compares well to $TMSCF_3$ (Ruppert's reagent), a reagent popularized by the Prakash group and others.[1] The reagent system has shown tremendous promise in the nucleophilic trifluoromethylation of: aldehydes and ketones,[2] imines,[3] disulfides and diselenides,[4] as well as cyclic sulfates.[5]



References: (1) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (2) (a) Pooput, C. et al. *J. Org. Chem.* **2006**, *71*, 3564. (b) Aït-Mohand, S. et al. *Org. Lett.* **2001**, *3*, 4271. (3) Xu, W.; Dolbier, W. R., Jr. *J. Org. Chem.* **2005**, *70*, 4741. (4) Pooput, C. et al. *Org. Lett.* **2004**, *6*, 301. (5) Takechi, N. et al. *Org. Lett.* **2002**, *4*, 4671.

Tetrakis(dimethylamino)ethylene NEW

TDAE
$C_{10}H_{24}N_4$
FW: 200.32
[*996-70-3*]

674613-1G	1 g
674613-10G	10 g

Trifluoroiodomethane, 99%

CF_3I
FW: 195.91
[*2314-97-8*]

171441-25G	25 g
171441-100G	100 g

Trimethyl(trifluoromethyl)silane, 99%

$C_4H_9F_3Si$
FW: 142.19
[*81290-20-2*]

488712-5ML	5 mL
488712-25ML	25 mL

Other Fluorination Reagents

Bis(2-methoxyethyl)aminosulfur trifluoride

$C_6H_{14}F_3NO_2S$
FW: 221.24
[*202289-38-1*]

494119-5G	5 g
494119-25G	25 g
494119-100G	100 g

Bis(2-methoxyethyl)aminosulfur trifluoride, 50% solution in toluene

$C_6H_{14}F_3NO_2S$
FW: 221.24
[*202289-38-1*]

94324-10ML-F	10 mL
94324-50ML-F	50 mL

Bis(2-methoxyethyl)aminosulfur trifluoride, 50% solution in tetrahydrofuran

$C_6H_{14}F_3NO_2S$
FW: 221.24
[*202289-38-1*]

94327-10ML-F	10 mL
94327-50ML-F	50 mL

(Diethylamino)sulfur trifluoride

$C_4H_{10}F_3NS$
FW: 161.19
[*38078-09-0*]

235253-1G	1 g
235253-5G	5 g
235253-25G	25 g

Morpholinosulfur trifluoride

$C_4H_8F_3NOS$
FW: 175.17
[*51010-74-3*]

338915-1G	1 g
338915-5G	5 g

N,N-Diethyl-1,1,2,3,3,3-hexafluoropropylamine

$C_7H_{11}F_6N$
FW: 223.16
[*309-88-6*]

564990-25G	25 g

Triethylamine trihydrofluoride, 98%

$C_6H_{18}F_3N$
FW: 161.21
[*73602-61-6*]

344648-5G	5 g
344648-25G	25 g
344648-100G	100 g

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)

$C_7H_{14}B_2ClF_9N_2$
FW: 354.26
[*140681-55-6*]

439479-5G	5 g
439479-25G	25 g
439479-100G	100 g

N-Fluorobenzenesulfonimide, 97%

$C_{12}H_{10}FNO_2S_2$
FW: 315.34
[*133745-75-2*]

392715-1G	1 g
392715-5G	5 g

1-Fluoropyridinium triflate, 99%

$C_6H_5F_4NO_3S$
FW: 247.17
[*107263-95-6*]

323659-1G	1 g
323659-5G	5 g

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