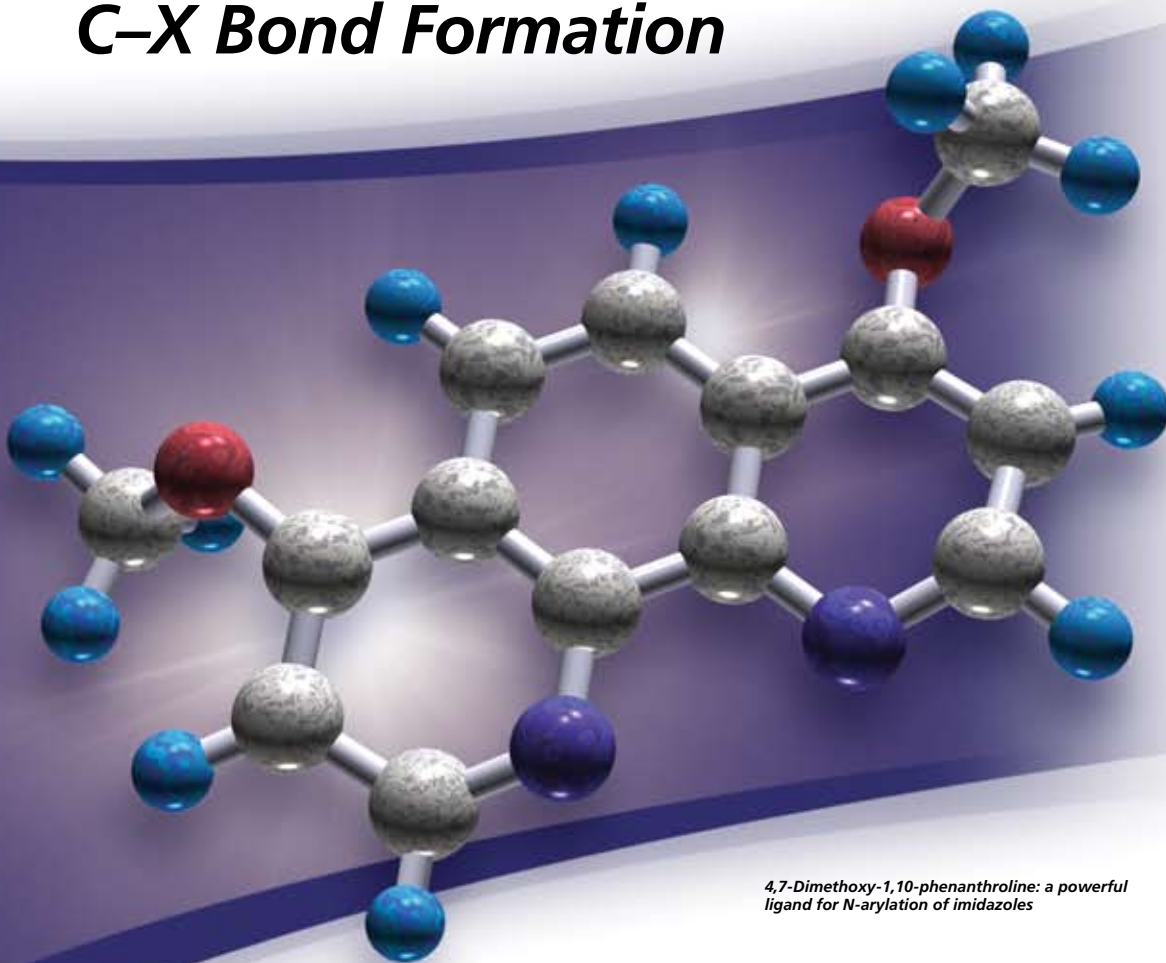


C-X Bond Formation



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

CLICK CHEMISTRY

TOOLS FOR
C-H AMINATION

KETONE AND ALDEHYDE
 α -OXYGENATION

BUCHWALD LIGANDS
FOR C-N COUPLING

HETEROATOM
FORMYLATION

MILD Mg-HALOGEN
EXCHANGE

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.

At Sigma-Aldrich, we are committed to be the preferred supplier for all of your research needs. If you cannot find a product for your research efforts in organic synthesis or drug discovery, we welcome your input. "Please Bother Us" with your suggestions at nwallock@sial.com or contact your local Sigma-Aldrich office.

It's Here! The NEW 2007–2008 Aldrich Handbook of Fine Chemicals

...featuring over 35,000 listings including 2,000 new products.

Order your FREE copy today!

- ✓ 35,000 Chemical Listings
- ✓ 10,000 Structures
- ✓ 2,000 NEW Products
- ✓ 6,100 Citations
- ✓ 3,000 Application Notes
- ✓ Enhanced Application Index
- ✓ Advanced Product Tables



Call 1-800-325-3010 (USA) to reserve your copy or visit sigma-aldrich.com/handbook24 today!

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.

Aldrich Chemical Co., Inc.
Sigma-Aldrich Corporation
6000 N. Teutonia Ave.
Milwaukee, WI 53209, USA

To Place Orders

Telephone 800-325-3010 (USA)
FAX 800-325-5052 (USA)

Customer & Technical Services

Customer Inquiries 800-325-3010
Technical Service 800-231-8327
SAFC™ 800-244-1173
Custom Synthesis 800-244-1173
Flavors & Fragrances 800-227-4563
International 414-438-3850
24-Hour Emergency 414-438-3850
Web Site sigma-aldrich.com
Email aldrich@sial.com

Subscriptions

To request your **FREE** subscription to *ChemFiles*, please contact us by:

Phone: 800-325-3010 (USA)

Mail: Attn: Marketing Communications
Aldrich Chemical Co., Inc.
Sigma-Aldrich Corporation
P.O. Box 355
Milwaukee, WI 53201-9358

Email: sams-usa@sial.com

International customers, please contact your local Sigma-Aldrich office. For worldwide contact information, please see back cover.

ChemFiles are also available in PDF format on the Internet at sigma-aldrich.com/chemfiles.

Aldrich brand products are sold through Sigma-Aldrich, Inc. Sigma-Aldrich, Inc. warrants that its products conform to the information contained in this and other Sigma-Aldrich publications. Purchaser must determine the suitability of the product for its particular use. See reverse side of invoice or packing slip for additional terms and conditions of sale.

All prices are subject to change without notice.

ChemFiles is a publication of Aldrich Chemical Co., Inc. Aldrich is a member of the Sigma-Aldrich Group. © 2007 Sigma-Aldrich Co.

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

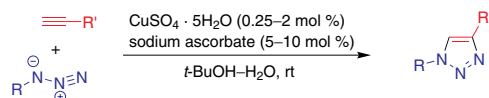
The use of a Cu(II) salt in the presence of an ascorbate reducing agent to form catalytically-active Cu(I) has been the method of choice for the preparative synthesis of 1,2,3-triazoles, but can be problematic in bioconjugation applications. A Cu(I) salt such as $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ 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 $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$ cleanly provides the cycloadduct in superb yield with complete control of regioselectivity (**Scheme 2**).⁴

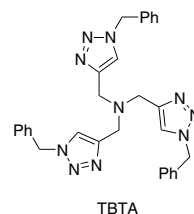
Of course, many organoazides are not commercially available. Carreira and co-workers recently reported the Co(II)-catalyzed hydroazidation of unactivated olefins with *p*-toluenesulfonyl azide (TsN_3) to yield alkyl azides (**Scheme 3**).⁵ The catalyst is easily prepared in situ from $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ 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) Tornøe, 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.

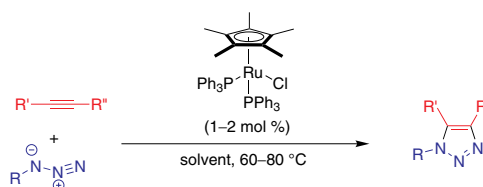


Scheme 1



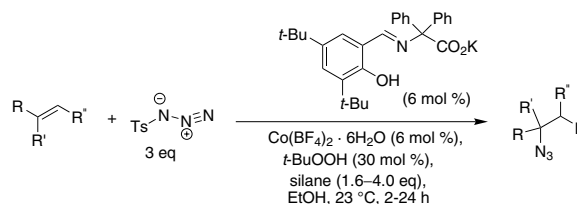
TBTA

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

Ready to scale up? For competitive quotes on larger quantities or custom synthesis, contact SAFC™ at 1-800-244-1173 (USA), or visit www.safglobal.com.

Copper(II) sulfate pentahydrate, ≥98.0%

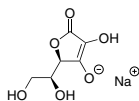
CuSO₄ · 5H₂O
 FW: 249.69
 [7758-99-8]

CuSO₄ · 5H₂O

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

(+)-Sodium L-ascorbate, ≥98%

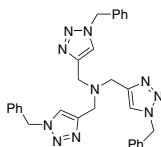
C₆H₇NaO₆
 FW: 198.11
 [134-03-2]



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

Tris(1-benzyl-1H-1,2,3-triazol-4-yl)methylamine, 97% NEW

TBTA
 C₃₀H₃₀N₁₀
 FW: 530.63



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

Pentamethylcyclopentadienylbis-(triphenylphosphine)ruthenium(II) chloride NEW

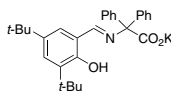
C₄₆H₄₅ClP₂Ru
 FW: 796.32
 [92361-49-4]



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

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

C₂₉H₃₂KNO₃
 FW: 481.67



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

Cobalt(II) tetrafluoroborate hexahydrate, 99%

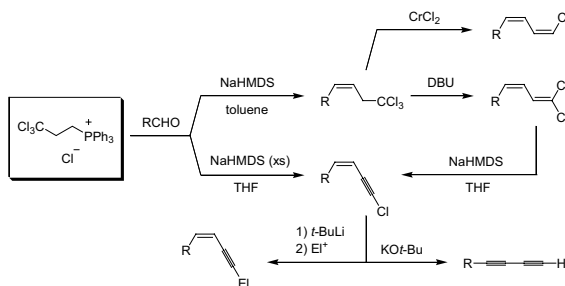
Co(BF₄)₂ · 6H₂O
 FW: 340.63
 [15684-35-2]

Co(BF₄)₂ · 6H₂O

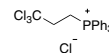
399957-25G	25 g
399957-100G	100 g

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**

C₂₁H₁₉Cl₄P
 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 guanidine themselves appear as structural elements in pharmacologically interesting substrates such as NK₁ receptor antagonists, toxins, and bromopyrrole metabolites (**Figure 1**).^{2b,2g}

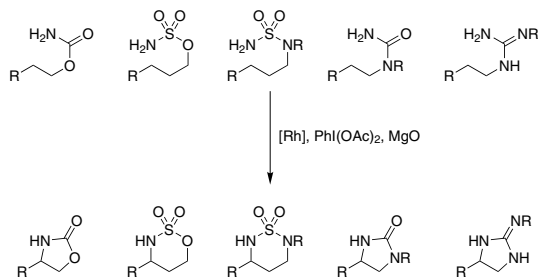
A variety of Rh-carboxylate catalysts exhibit at least some effectiveness in the urea and guanidine cyclizations, but the most promising results are obtained using the combination of catalytic Rh₂(esp)₂ with substrates bearing 2,2,2-trichloroethoxysulfonyl (Tces) protection at nitrogen. Installation 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 Rh₂(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 the reaction of an amine with one of two reagents derived from *S,S*-dimethyl-*N*-(2,2,2-trichloroethoxysulfonyl)carbonimidodithionate (**Scheme 4**).

The isothiurea 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 pseudothiurea 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

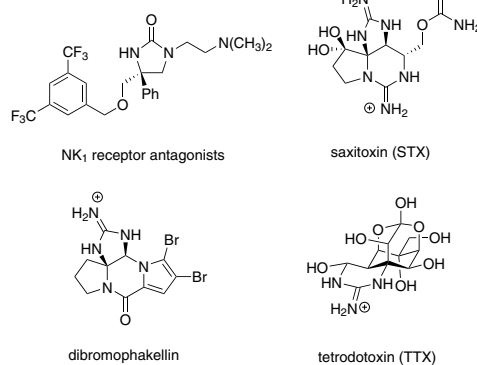
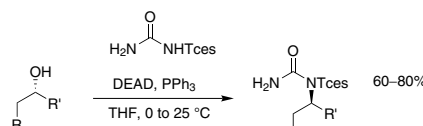
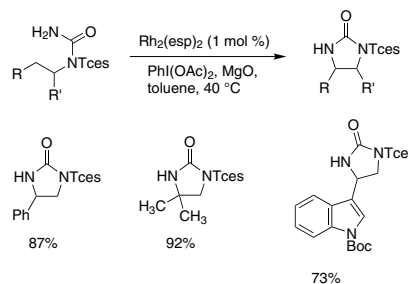


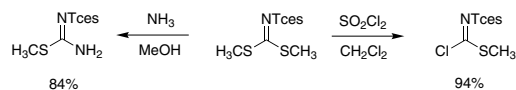
Figure 1



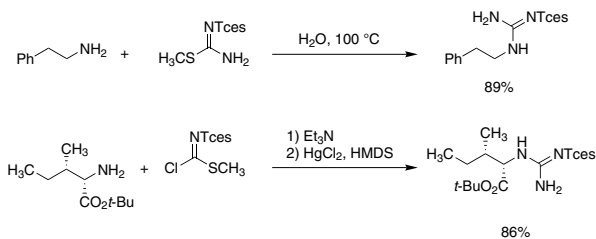
Scheme 2



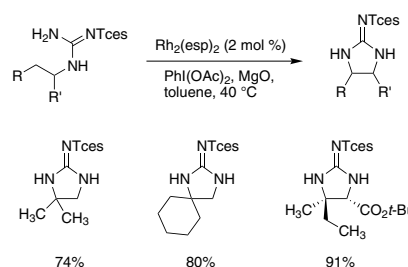
Scheme 3



Scheme 4



Scheme 5

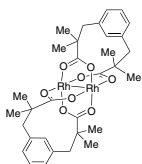


Scheme 6

Bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)], 96%

NEW

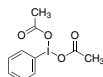
Rh₂(esp)₂
 C₃₂H₄₀O₈Rh₂
 FW: 758.47
 [819050-89-0]



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

(Diacetoxyido)benzene, 98%

C₁₀H₁₁O₄
 FW: 322.1
 [3240-34-4]

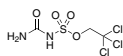


178721-5G	5 g
178721-25G	25 g
178721-100G	100 g

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

NEW

Tces-urea
 C₃H₅Cl₃N₂O₄S
 FW: 271.51

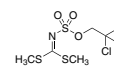


680834-1G	1 g
680834-5G	5 g

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

NEW

C₅H₈Cl₃NO₃S₃
 FW: 332.68

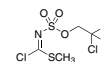


679879-1G	1 g
679879-5G	5 g

S-Methyl N-(2,2,2-trichloroethoxysulfonyl)-carbonylchloroimidothioate

NEW

C₄H₅Cl₃NO₃S₂
 FW: 321.03

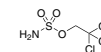


679712-1G	1 g
679712-5G	5 g

2,2,2-Trichloroethoxysulfonamide, 97%

NEW

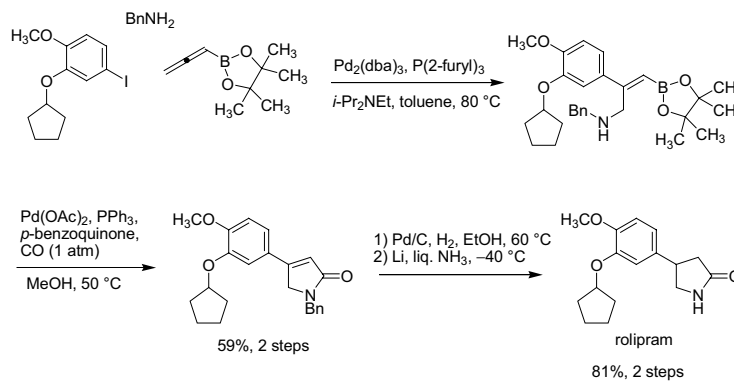
Tces-NH₂
 C₂H₄Cl₃NO₃S
 FW: 228.48
 [69226-51-3]



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.

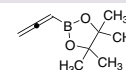


References: (1) (a) Tonogaki, K. et al. *Org. Lett.* **2006**, *8*, 1419.
 (b) Tonogaki, K. et al. *J. Am. Chem. Soc.* **2006**, *128*, 1464. (c) Bustelo, E. et al. *J. Am. Chem. Soc.* **2005**, *127*, 11582.

Allenylboronic acid pinacol ester, 97%

NEW

C₉H₁₅BO₂
 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 aldehydes² and ketones³ 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.

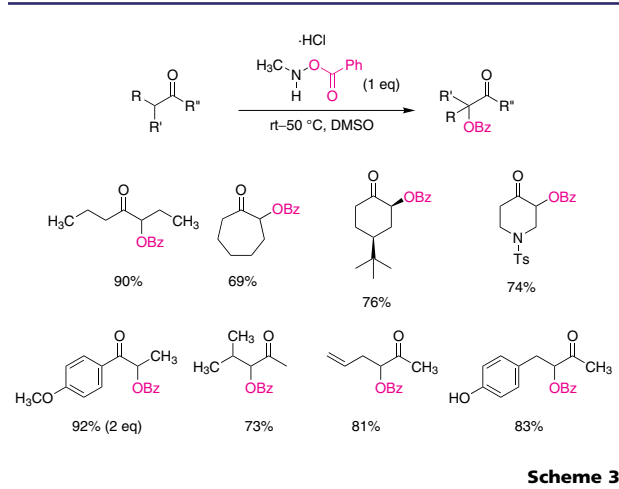
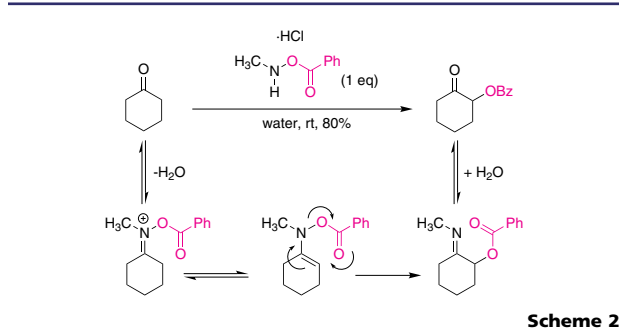
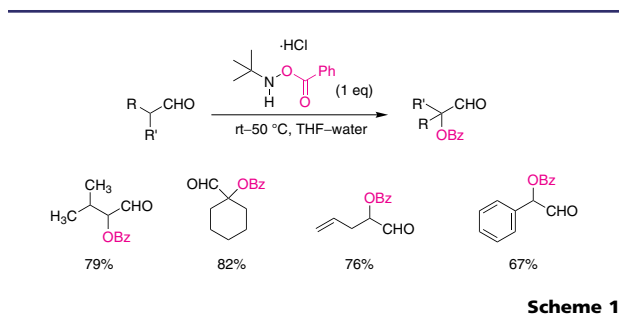
Nicholas Tomkinson of Cardiff University (UK) recently reported several practical reagents for the preparation of α -oxygenated carbonyl compounds.⁴ *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochloride is a bench stable reagent for the α -functionalization of a variety of aldehydes under mild conditions (**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 regioselectively at the more substituted carbon. In addition to water and DMSO, THF and CHCl_3 can be used as solvents with similar yields.

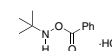
Sigma-Aldrich is delighted to add these new tools to our ever-growing arsenal of oxidation reagents.

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.



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

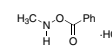
$\text{C}_{11}\text{H}_{16}\text{ClNO}_2$
FW: 229.70



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

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

$\text{C}_8\text{H}_{10}\text{ClNO}_2$
FW: 187.62



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

Monthly Chemistry E-Newsletter

Got ChemNews?

sigma-aldrich.com/chemnews



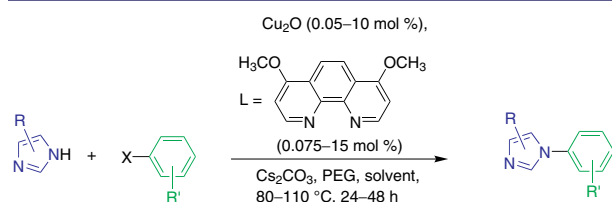
Ready to scale up? For competitive quotes on larger quantities or custom synthesis, contact SAFC™ at 1-800-244-1173 (USA), or visit www.safglobal.com.

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 iodide (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**).

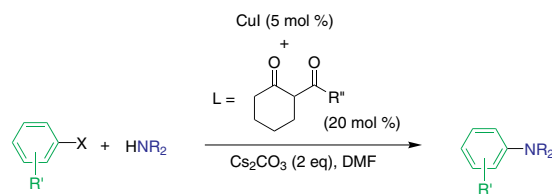
The Buchwald group has also made significant advances in the area of mild Ullmann-type couplings of aryl halides with primary and secondary amines in the presence of CuI and a β -diketone ligand (**Scheme 2**).² Heterocyclic structures may be present in either coupling partner, and a variety of functional 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	<i>n</i> -PrCN	95
2		I	5/7.5	CH ₃ CN	95
3		Br	10/15	<i>n</i> -PrCN	92
4		I	5/7.5	<i>n</i> -PrCN	94
5		I	5/7.5	<i>n</i> -PrCN	94
6		I	5/7.5	<i>n</i> -PrCN	84
7		Br	10/15	<i>n</i> -PrCN	95
8		I	5/7.5	<i>n</i> -PrCN	85

Scheme 1

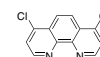


Entry	Product	X	R''	Yield (%)
1		I	CH ₃	94
2		I	<i>i</i> -Pr	96
3		I	CH ₃	98
4		I	<i>i</i> -Pr	99
5		I	<i>i</i> -Pr	90
6		I	<i>i</i> -Pr	83
7		Br	<i>i</i> -Pr	89

Scheme 2

4,7-Dichloro-1,10-phenanthroline

C₁₂H₈Cl₂N₂
FW: 249.10

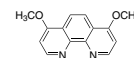


678015-250MG
678015-1G

250 mg
1 g

4,7-Dimethoxy-1,10-phenanthroline

C₁₄H₁₂N₂O₂
FW: 240.26
[92149-07-0]



678023-250MG
678023-1G

250 mg
1 g

2-Acetylcyclohexanone, 97%

C₈H₁₂O₂
FW: 140.18
[874-23-7]



179760-5G
179760-25G

5 g
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 cyanomethylformate⁴) 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.; Benoit, 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) Duczak, 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.

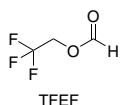
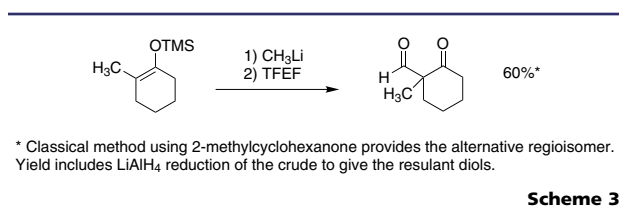
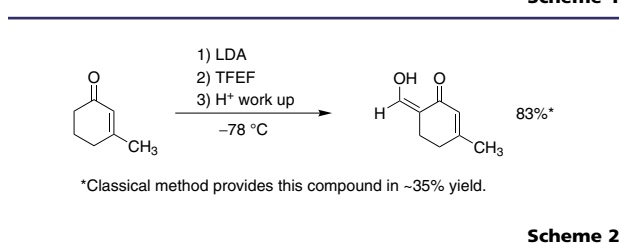
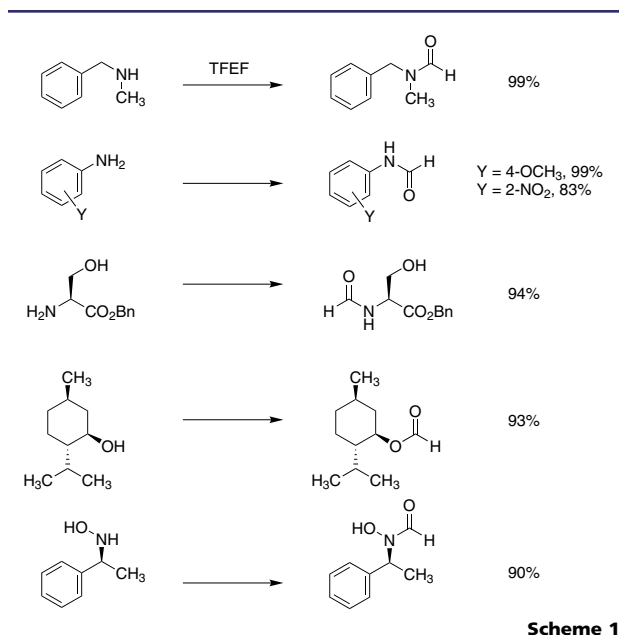


Figure 1



2,2,2-Trifluoroethyl formate, 95%

NEW

TFEF
C₃H₃F₃O₂
FW: 128.05
[32042-38-9]



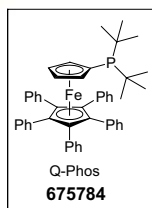
669083-1G

1 g

669083-5G

5 g

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



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.

Ready to scale up? For competitive quotes on larger quantities or custom synthesis, contact SAFC™ at 1-800-244-1173 (USA), or visit www.safglobal.com.

Order: 1.800.325.3010 Technical Services: 1.800.231.8327

Heteroatom Formylation

ALDRICH

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.

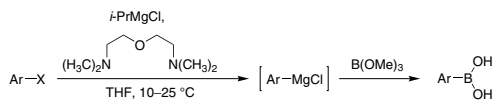
The combination of *i*-PrMgCl and the tridentate ligand bis[2-(*N,N*-dimethylamino)ethyl] ether has proven to be an excellent reagent system for non-cryogenic Grignard formation from aryl bromides and iodides bearing sensitive functional groups.² Subsequent reaction with an electrophile such as trimethylborate 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.

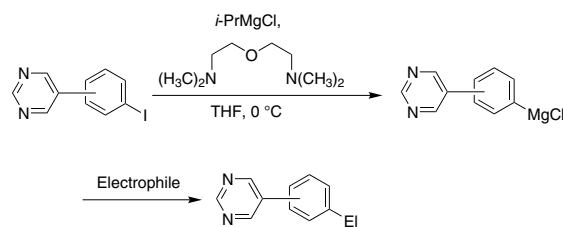
Using this methodology, a diverse set of aryl ketones were prepared in high yield from the corresponding aryl acid chlorides (**Figure 1**). These examples also illustrate the excellent functional group tolerance observed under the reactions conditions.

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.



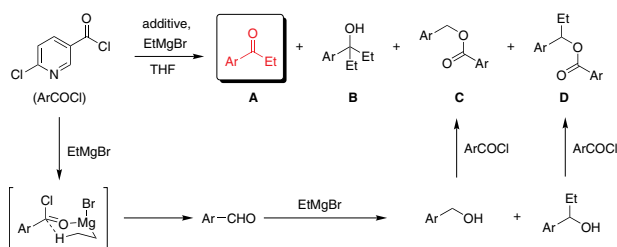
Entry	Aryl halide	Boronic acid	Yield (%)	Yield with no ligand (%)
1			86	28
2			77	28
3			85	82
4			76	69
5			70	–

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

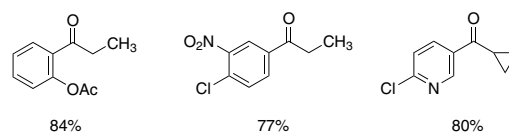


Figure 1

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

NEW

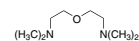
BDAEE

C₈H₂₀N₂O

FW: 160.26

[3033-62-3]

667609-100ML



667609-500ML

100 mL

500 mL

Isopropylmagnesium chloride, 2.0 M in tetrahydrofuran

C₃H₇MgCl

FW: 102.85

[1068-55-9]



230111-100ML

100 mL

230111-800ML

800 mL

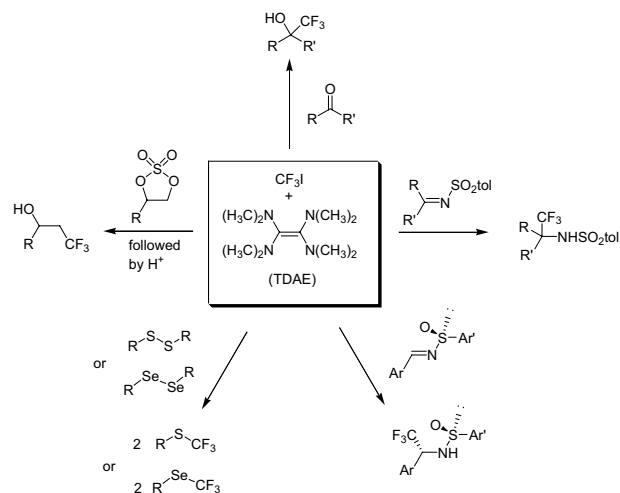
TO ORDER: Contact your local Sigma-Aldrich office (see back cover), call 1-800-325-3010 (USA), or visit sigma-aldrich.com/chemicalsynthesis.

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 $\text{CF}_3\text{I}/\text{TDAE}$ reagent system is compared 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) Ait-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

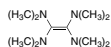
NEW

TDAE

$\text{C}_{10}\text{H}_{24}\text{N}_4$

FW: 200.32

[996-70-3]



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

Trifluoriodomethane, 99%

CF_3I

FW: 195.91

[2314-97-8]



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

Trimethyl(trifluoromethyl)silane, 99%

$\text{C}_4\text{H}_9\text{F}_3\text{Si}$

FW: 142.19

[81290-20-2]



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

Other Fluorination Reagents

Bis(2-methoxyethyl)aminosulfur trifluoride

$\text{C}_6\text{H}_{14}\text{F}_3\text{NO}_2\text{S}$

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

$\text{C}_6\text{H}_{14}\text{F}_3\text{NO}_2\text{S}$

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

$\text{C}_6\text{H}_{14}\text{F}_3\text{NO}_2\text{S}$

FW: 221.24

[202289-38-1]



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

(Diethylamino)sulfur trifluoride

$\text{C}_4\text{H}_{10}\text{F}_3\text{NS}$

FW: 161.19

[38078-09-0]



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

Morpholinosulfur trifluoride

$\text{C}_4\text{H}_8\text{F}_3\text{NOS}$

FW: 175.17

[51010-74-3]



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

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

$\text{C}_7\text{H}_{11}\text{F}_6\text{N}$

FW: 223.16

[309-88-6]



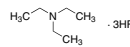
564990-25G	25 g
------------	------

Triethylamine trihydrofluoride, 98%

$\text{C}_6\text{H}_{18}\text{F}_3\text{N}$

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)

$\text{C}_7\text{H}_{14}\text{B}_2\text{ClF}_9\text{N}_2$

FW: 354.26

[140681-55-6]



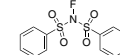
439479-5G	5 g
439479-25G	25 g
439479-100G	100 g

N-Fluorobenzenesulfonimide, 97%

$\text{C}_{12}\text{H}_{10}\text{FNO}_2\text{S}_2$

FW: 315.34

[133745-75-2]



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

1-Fluoropyridinium triflate, 99%

$\text{C}_6\text{H}_5\text{F}_4\text{NO}_3\text{S}$

FW: 247.17

[107263-95-6]



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

Argentina

SIGMA-ALDRICH DE ARGENTINA S.A.
Free Tel: 0810 888 7446
Tel: (+54) 11 4556 1472
Fax: (+54) 11 4552 1698

Australia

SIGMA-ALDRICH PTY LTD.
Free Tel: 1800 800 097
Free Fax: 1800 800 096
Tel: (+61) 2 9841 0555
Fax: (+61) 2 9841 0500

Austria

SIGMA-ALDRICH HANDELS GmbH
Tel: (+43) 1 605 81 10
Fax: (+43) 1 605 81 20

Belgium

SIGMA-ALDRICH NV/SA.
Free Tel: 0800 14747
Free Fax: 0800 14745
Tel: (+32) 3 899 13 01
Fax: (+32) 3 899 13 11

Brazil

SIGMA-ALDRICH BRASIL LTDA.
Free Tel: 0800 701 7425
Tel: (+55) 11 3732 3100
Fax: (+55) 11 5522 9895

Canada

SIGMA-ALDRICH CANADA LTD.
Free Tel: 1800 565 1400
Free Fax: 1800 265 3858
Tel: (+1) 905 829 9500
Fax: (+1) 905 829 9292

China

SIGMA-ALDRICH (SHANGHAI)
TRADING CO. LTD.
Free Tel: 800 819 3336
Tel: (+86) 21 6141 5566
Fax: (+86) 21 6141 5567

Czech Republic

SIGMA-ALDRICH S.R.O.
Tel: (+420) 246 003 200
Fax: (+420) 246 003 291

Denmark

SIGMA-ALDRICH DENMARK A/S
Tel: (+45) 43 56 59 10
Fax: (+45) 43 56 59 05

Finland

SIGMA-ALDRICH FINLAND OY
Tel: (+358) 9 350 9250
Fax: (+358) 9 350 92555

France

SIGMA-ALDRICH CHIMIE S.à.r.l.
Free Tel: 0800 211 408
Free Fax: 0800 031 052
Tel: (+33) 474 82 28 00
Fax: (+33) 474 95 68 08

Germany

SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800 51 55 000
Free Fax: 0800 64 90 000
Tel: (+49) 89 6513 0
Fax: (+49) 89 6513 1160

Greece

SIGMA-ALDRICH (O.M.) LTD.
Tel: (+30) 210 994 8010
Fax: (+30) 210 994 3831

Hungary

SIGMA-ALDRICH Kft
Ingyenes zöld telefon: 06 80 355 355
Ingyenes zöld fax: 06 80 344 344
Tel: (+36) 1 235 9055
Fax: (+36) 1 235 9050

India

SIGMA-ALDRICH CHEMICALS
PRIVATE LIMITED
Telephone
Bangalore: (+91) 80 6621 9600
New Delhi: (+91) 11 4165 4255
Mumbai: (+91) 22 2570 2364
Hyderabad: (+91) 40 6684 5488
Fax
Bangalore: (+91) 80 6621 9650
New Delhi: (+91) 11 4165 4266
Mumbai: (+91) 22 2579 7589
Hyderabad: (+91) 40 6684 5466

Ireland

SIGMA-ALDRICH IRELAND LTD.
Free Tel: 1800 200 888
Free Fax: 1800 600 222
Tel: (+353) 1 404 1900
Fax: (+353) 1 404 1910

Israel

SIGMA-ALDRICH ISRAEL LTD.
Free Tel: 1 800 70 2222
Tel: (+972) 8 948 4100
Fax: (+972) 8 948 4200

Italy

SIGMA-ALDRICH S.r.l.
Numero Verde: 800 827018
Tel: (+39) 02 3341 7310
Fax: (+39) 02 3801 0737

Japan

SIGMA-ALDRICH JAPAN K.K.
Tokyo Tel: (+81) 3 5796 7300
Tokyo Fax: (+81) 3 5796 7315

Korea

SIGMA-ALDRICH KOREA
Free Tel: (+82) 80 023 7111
Free Fax: (+82) 80 023 8111
Tel: (+82) 31 329 9000
Fax: (+82) 31 329 9090

Malaysia

SIGMA-ALDRICH (M) SDN. BHD
Tel: (+60) 3 5635 3321
Fax: (+60) 3 5635 4116

Mexico

SIGMA-ALDRICH QUÍMICA, S.A. de C.V.
Free Tel: 01 800 007 5300
Free Fax: 01 800 712 9920
Tel: 52 722 276 1600
Fax: 52 722 276 1601

The Netherlands

SIGMA-ALDRICH CHEMIE BV
Free Tel: 0800 022 9088
Free Fax: 0800 022 9089
Tel: (+31) 78 620 5411
Fax: (+31) 78 620 5421

New Zealand

SIGMA-ALDRICH NEW ZEALAND LTD.
Free Tel: 0800 936 666
Free Fax: 0800 937 777
Tel: (+61) 2 9841 0555
Fax: (+61) 2 9841 0500

Norway

SIGMA-ALDRICH NORWAY AS
Tel: (+47) 23 17 60 60
Fax: (+47) 23 17 60 50

Poland

SIGMA-ALDRICH Sp. z o.o.
Tel: (+48) 61 829 01 00
Fax: (+48) 61 829 01 20

Portugal

SIGMA-ALDRICH QUÍMICA, S.A.
Free Tel: 800 202 180
Free Fax: 800 202 178
Tel: (+351) 21 924 2555
Fax: (+351) 21 924 2610

Russia

SIGMA-ALDRICH RUS, LLC
Tel: +7 (495) 621 6037
Fax: +7 (495) 621 5923

Singapore

SIGMA-ALDRICH PTE. LTD.
Tel: (+65) 6779 1200
Fax: (+65) 6779 1822

South Africa

SIGMA-ALDRICH
SOUTH AFRICA (PTY) LTD.
Free Tel: 0800 1100 75
Free Fax: 0800 1100 79
Tel: (+27) 11 979 1188
Fax: (+27) 11 979 1119

Spain

SIGMA-ALDRICH QUÍMICA, S.A.
Free Tel: 900 101 376
Free Fax: 900 102 028
Tel: (+34) 91 661 99 77
Fax: (+34) 91 661 96 42

Sweden

SIGMA-ALDRICH SWEDEN AB
Tel: (+46) 8 742 4200
Fax: (+46) 8 742 4243

Switzerland

SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800 80 00 80
Free Fax: 0800 80 00 81
Tel: (+41) 81 755 2828
Fax: (+41) 81 755 2815

United Kingdom

SIGMA-ALDRICH COMPANY LTD.
Free Tel: 0800 717 181
Free Fax: 0800 378 785
Tel: (+44) 1747 833 000
Fax: (+44) 1747 833 313
SAFC (UK) Free Tel: 0800 71 71 17

United States

SIGMA-ALDRICH
P.O. Box 14508
St. Louis, Missouri 63178
Toll-Free: 800 325 3010
Toll-Free Fax: 800 325 5052
Call Collect: (+1) 314 771 5750
Tel: (+1) 314 771 5765
Fax: (+1) 314 771 5757

Internet

sigma-aldrich.com

World Headquarters

3050 Spruce St., St. Louis, MO 63103
(314) 771-5765
sigma-aldrich.com

Order/Customer Service (800) 325-3010 • Fax (800) 325-5052

Technical Service (800) 325-5832 • sigma-aldrich.com/techservice

Development/Bulk Manufacturing Inquiries SAFC™ (800) 244-1173

The SIGMA-ALDRICH Group

©2007 Sigma-Aldrich Co. All rights reserved.

SIGMA, SAFC, SAFC™, SIGMA-ALDRICH, ISOTEC, ALDRICH, FLUKA, and SUPELCO are trademarks belonging to Sigma-Aldrich Co. and its affiliate Sigma-Aldrich Biotechnology, L.P. Riedel-de Haën® trademark under license from Riedel-de Haën GmbH. Sigma brand products are sold through Sigma-Aldrich, Inc. Sigma-Aldrich, Inc. warrants that its products conform to the information contained in this and other Sigma-Aldrich publications. Purchaser must determine the suitability of the product(s) for their particular use. Additional terms and conditions may apply. Please see reverse side of the invoice or packing slip.



*Accelerating Customers' Success
through Leadership in Life Science,
High Technology and Service*

SIGMA-ALDRICH™

3050 Spruce Street • St. Louis, MO 63103 USA

Return Service Requested

JEL
01838-503201
0017