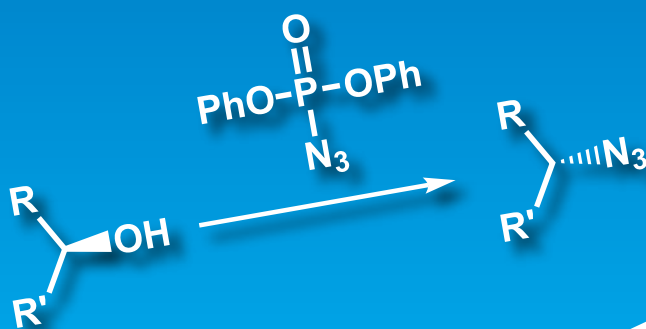
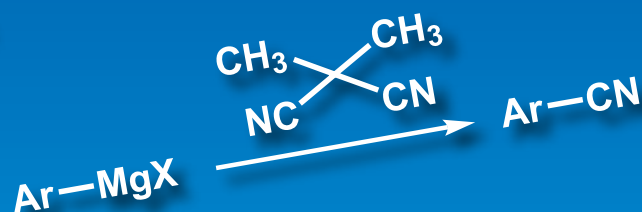
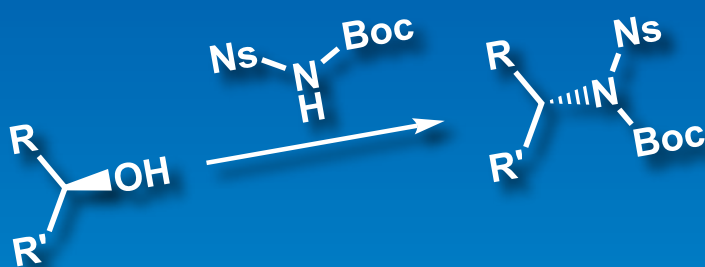


# C-N Bond Formation Reactions



Reagents for Amination

Reagents for Nitration

Reagents for Cyanation

Reagents for Azidation and Diazotization

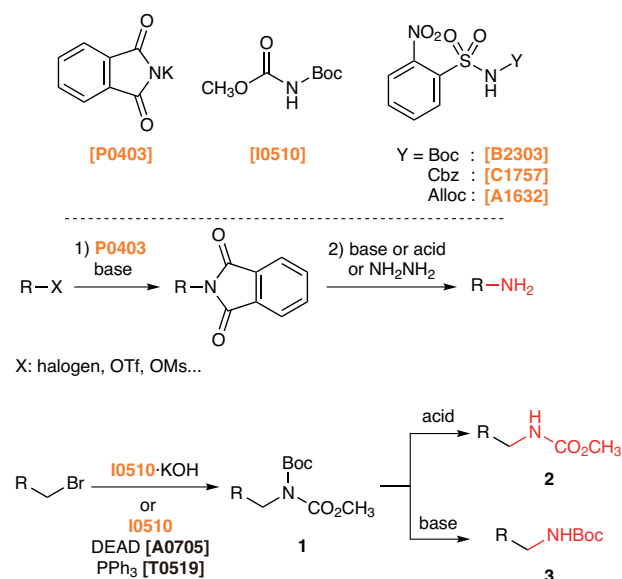
Reagents for Guanidinylation

# C-N Bond Formation Reactions

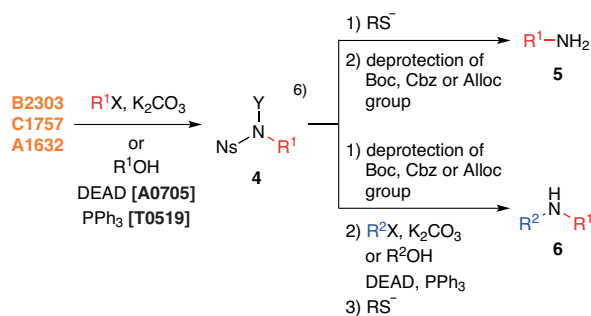
Nitrogen-containing compounds are found in wide fields from natural products such as amino acids, nucleic acids and alkaloids to synthetic compounds such as electronic materials and polyamides. Furthermore, various kinds of nitrogen-containing functional groups are known such as amino groups and nitro groups, which have different coupling schemes and oxidation states. Therefore, C-N bond formation reactions vary with each functional group. Since it is hard to introduce C-N bond formation reactions comprehensively because these reactions encompass many methods from simple introduction of functional groups to the construction of heterocyclic rings, this brochure mainly introduces TCI's reagents for installation of nitrogen-containing functional groups among the reagents for C-N bond formation reactions. Additionally, there are some cyanating agents in this brochure that may look strange to apply to C-N bond formation reactions, but these reagents are introduced because the cyano group can be converted into other nitrogen-containing functional groups.

## ● Reagents for Amination

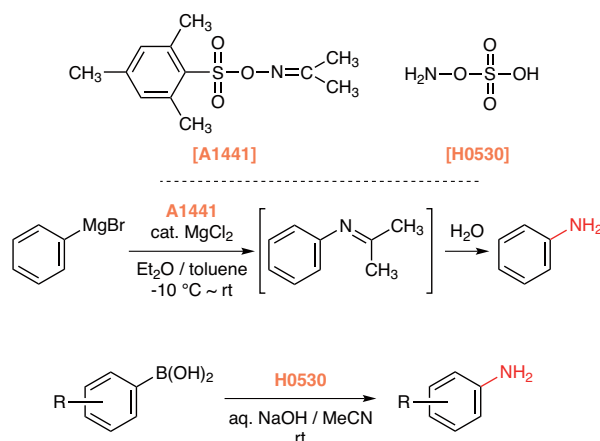
The Gabriel amine synthesis<sup>1)</sup> is widely used as a nucleophilic amination reaction and potassium phthalimide and similar aminating agents have been reported so far. The potassium salt of *tert*-butyl methyl iminodicyanoacetate [I0510] reacts with an alkyl halide to give an imide 1.<sup>2)</sup> 1 affords *N*-methoxycarbonylamine 2 and *N*-Boc amine 3 by treatment with acid or base, respectively. Furthermore, I0510 can be applied to the Mitsunobu reaction and convert a hydroxy group into an amino group.<sup>3)</sup>



Meanwhile, Fukuyama *et al.* reported another method of amine synthesis using sulfonamides [B2303] [C1757] [A1632], which are protected by the *o*-nitrobenzenesulfonyl (Ns) group.<sup>4)</sup> These products afford the protected amines 4 under basic conditions with alkyl halides or under Mitsunobu conditions with alcohols, respectively. Each protective group is selectively removed and the primary amine 5 is given by the removal of both protecting groups. However, when the Ns group of 4 is left remaining, the secondary amine 6 can be given after alkylation and successive removal of it.

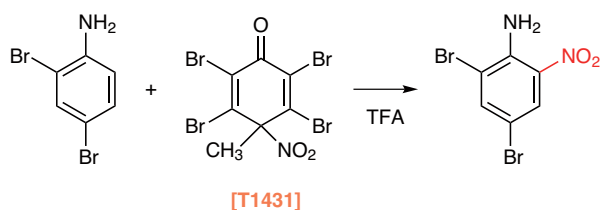


Acetoxime O-(2,4,6-trimethylphenylsulfonate) [A1441] is regarded as an electrophilic aminating reagent.<sup>6)</sup> A1441 reacts with Grignard reagents under a catalytic amount of magnesium chloride to give primary amines in good yields.<sup>7)</sup> Furthermore, hydroxylamine-O-sulfonic acid (HSA) [H0530] is also utilized as an aminating reagent. HSA behaves as an amination and gives primary anilines by the treatment with phenylboron derivatives. It is also an advantage that the reaction can proceed without any transition metal catalysts and with easy handling.<sup>8)</sup>



## ● Reagents for Nitration

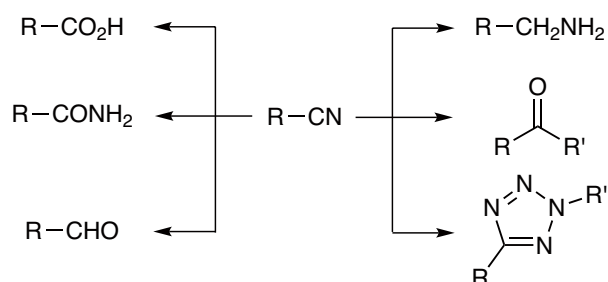
The nitro group is a strong electron-withdrawing functional group which can decrease the electron density of aromatic rings and increase the acidity of the proton at the  $\alpha$ -position of the nitroalkane. Therefore, compounds with nitro groups can undergo unique reactions such as the Henry reaction and the Nef reaction. Generally, nitration of an aromatic ring is proceeded by electrophilic substitution reaction with concentrated nitric acid and concentrated sulfuric acid. However, 2,3,5,6-tetrabromo-4-methyl-4-nitro-2,5-cyclohexadien-1-one [T1431] is a mild nitrating reagent for aromatic compounds.<sup>9,10</sup> For instance, electron-rich aromatic compounds like anilines give nitrated compounds substituted at the *ortho*- or *para*-position by treatment with T1431.



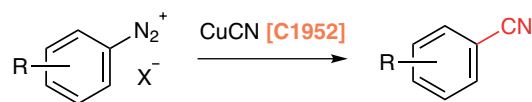
## ● Reagents for Cyanation

The cyano group is a strong electron-withdrawing group and a number of cyanating reagents are widely used in organic synthesis. The cyano group is converted to other functional groups such as carboxylic acids or amides by hydrolysis, and is also converted to amines or aldehydes by reduction with some reducing reagents. Furthermore, nitriles are transformed into the corresponding asymmetric ketones through nucleophilic addition reactions with Grignard reagents or organolithiums. On the other hand, the cyano group can be used for cycloaddition reactions with other multiple bonds. For instance, alkyl nitriles are cyclized with azides to give tetrazoles.

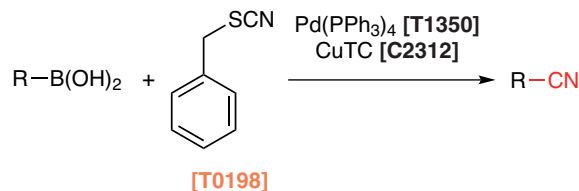
To introduce the cyano group, the reaction of potassium cyanide [P1613] with alkyl halides is a typical synthetic method and the copper cyanide-mediated Sandmeyer reaction and the Rosenmund-von Braun reaction have been known for a long time. Recently, cyanation reactions using palladium catalysts with some cyanating reagents have been developed. Benzyl thiocyanate [T0198],<sup>11</sup> ethyl cyanoacetate [C0441],<sup>12</sup> *tert*-butyl isocyanide [B1274]<sup>13</sup> and acetone cyanohydrin [M0361]<sup>14</sup> work as cyanide ion equivalents. Recently, some groups have reported that acetonitrile<sup>15</sup> and dimethylmalononitrile<sup>16</sup> [D5514] can be utilized as cyano sources. In this way, a variety of cyanating reagents are used for the direct cyanation of various substances.



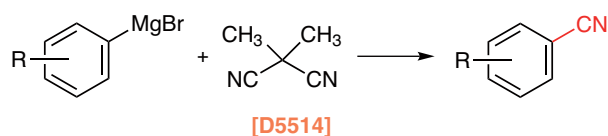
## Sandmeyer reaction



## Pd-Catalyzed cross-coupling cyanation

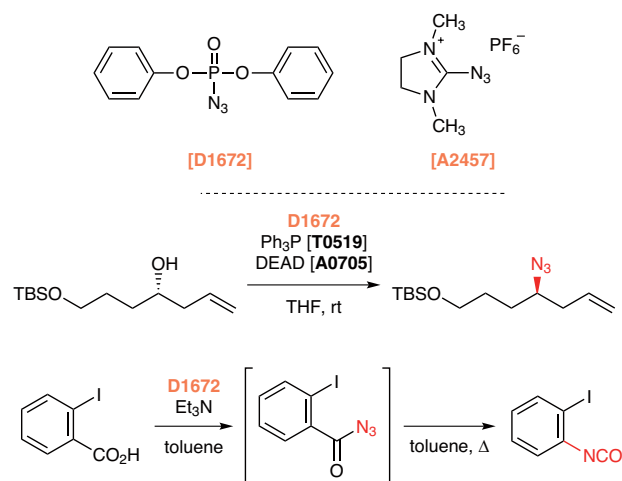


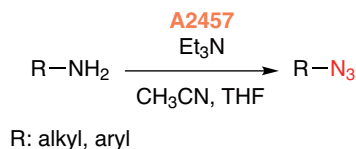
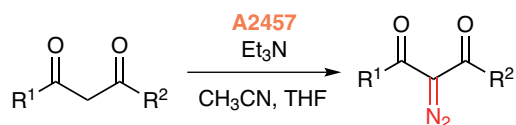
## Cyanation of Grignard reagent



## ● Reagents for Azidation and Diazotization

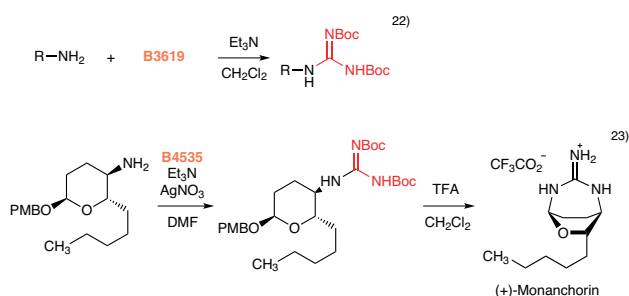
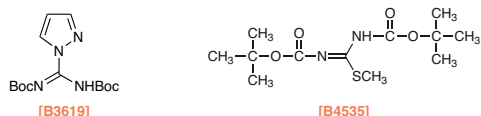
Organic azide compounds can be synthesized in a simple manner by the reaction of sodium azide [S0489] with halogenated alkyl compounds, or the reaction with trifluoromethanesulfonyl azide and primary amines. However, these azide sources have highly explosive characters, which makes them difficult to handle. In contrast, Shioiri *et al.* developed a stable and easy-to-handle reagent for azidation, DPPA [D1672].<sup>17</sup> When an alcohol is treated with DPPA under Mitsunobu conditions, the inverted azide compound is given in high yield. DPPA is utilized not only in the Curtius rearrangement but also as a condensation reagent.<sup>18</sup> Furthermore, 2-azido-1,3-dimethylimidazolium hexafluorophosphate (ADMP) [A2457], which was developed by Kitamura *et al.*, is a crystalline diazotransfer reagent with high thermal stability and low reactivity to impact and friction. ADMP reacts with a variety of primary amines to afford azides<sup>19</sup> as well as with 1,3-dicarbonyl compounds to afford  $\alpha$ -diazo compounds in high yields.<sup>20</sup>





## ● Reagents for Guanidinylation

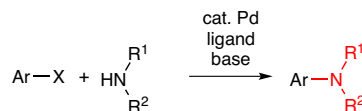
The guanidine moiety has a stronger basicity among organic bases and it is seen in many kinds of bioactive compounds as well as in arginine. For instance, saxitoxin and tetrodotoxin derived from puffer toxin, and batzelladine A as an HIV inhibitor in sea sponge are known as compounds bearing a guanidino group. Furthermore, pharmaceutical compounds like antimalarial and antimicrobial agents often contain guanidine structures. In this way, guanidinylation reagents are utilized in the synthesis of guanidine derivatives in the drug discovery field.<sup>21)</sup> The guanidinylation group is mainly introduced by an addition reaction to an amino group.



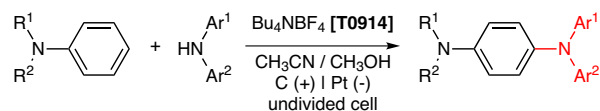
## ● C-N bond formation via Cross-Coupling Reaction

Buchwald<sup>24)</sup> and Hartwig<sup>25)</sup> have independently reported a new type of coupling reaction between amines and aryl halides in the presence of palladium catalyst and strong base. This reaction is called the Buchwald-Hartwig cross-coupling reaction. This reaction introduces amino groups to aromatic compounds but it can also be applied to the construction of nitrogen-containing heteroaromatic rings.<sup>26)</sup> Therefore, the reaction is widely used in the total synthesis of natural products, medicinal chemistry and process chemistry. Very recently, the new electro-oxidative C-N cross-coupling reaction has been reported.<sup>27)</sup> This reaction has some advantages: *para*-selective cross-coupling; metal-catalyst free reaction; and being regarded as a green reaction since the sole byproduct is hydrogen gas generated through C-H activation.

### Buchwald-Hartwig cross-coupling



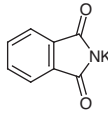
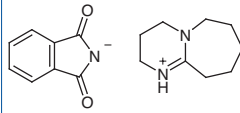
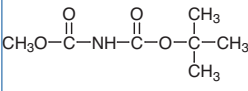
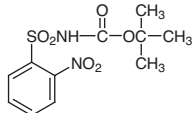
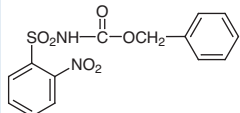
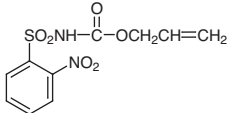
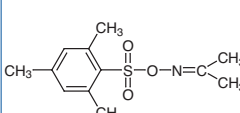
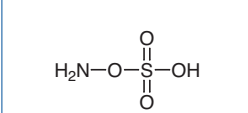
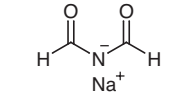
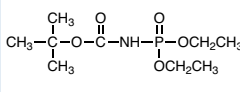
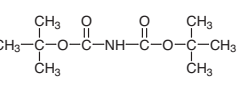
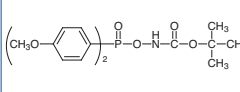
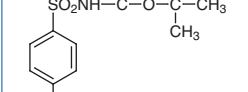
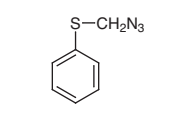
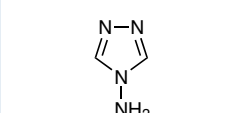
### Electrooxidative C-N cross-coupling



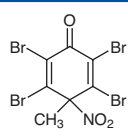
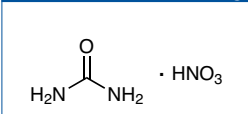
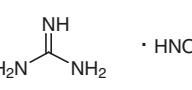
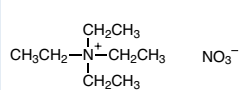
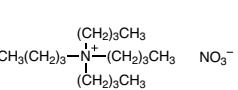
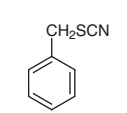
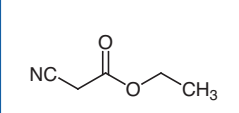
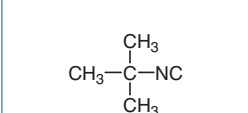
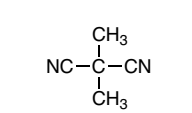
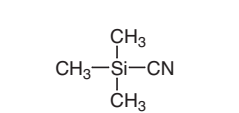
## References

- 1) a) S. Gabriel, *Ber.* **1887**, *20*, 2224.  
b) M. S. Gibson, R. W. Bradshaw, *Angew. Chem. Int. Ed.* **1968**, *7*, 919.
- 2) a) J. D. Elliott, J. H. Jones, *J. Chem. Soc., Chem. Commun.* **1977**, 758.  
b) C. T. Clarke, J. D. Elliott, J. H. Jones, *J. Chem. Soc., Perkin Trans. 1* **1978**, 1088.
- 3) J. M. Chong, S. B. Park, *J. Org. Chem.* **1993**, *58*, 7300.
- 4) T. Fukuyama, M. Cheung, T. Kan, *Synlett* **1999**, 1301.
- 5) T. Kan, A. Fujiwara, H. Kobayashi, T. Fukuyama, *Tetrahedron* **2002**, *58*, 6267.
- 6) E. Erdik, M. Ay, *Syn. React. Inorg. Met.* **1988**, *19*, 663.
- 7) E. Erdik, *e-EROS* **2001**.
- 8) S. Voth, J. W. Hollett, J. A. McCubbin, *J. Org. Chem.* **2015**, *80*, 2545.
- 9) a) M. Lemaire, A. Guy, J. Roussel, J.-P. Guette, *Tetrahedron* **1987**, *43*, 835.  
b) M. Lemaire, A. Guy, P. Boutin, J.-P. Guette, *Synthesis* **1989**, 761.
- 10) R. G. Coombes, J. H. Ridd, *J. Chem. Soc., Chem. Commun.* **1992**, 174.
- 11) Z. Zhang, L. S. Liebeskind, *Org. Lett.* **2006**, *8*, 4331.
- 12) S. Zheng, C. Yu, Z. Shen, *Org. Lett.* **2012**, *14*, 3644.
- 13) J. Peng, J. Zhao, Z. Hu, D. Liang, J. Huang, Q. Zhu, *Org. Lett.* **2012**, *14*, 4966.
- 14) K. J. Powell, L.-C. Han, P. Sharma, J. E. Moses, *Org. Lett.* **2014**, *16*, 2158.
- 15) Y. Zhu, M. Zhao, W. Lu, L. Li, Z. Shen, *Org. Lett.* **2015**, *17*, 2602.
- 16) a) J. T. Reeves, C. A. Malapit, F. G. Buono, K. P. Sidhu, M. A. Marsini, C. A. Sader, K. R. Fandrick, C. A. Busacca, C. H. Senanayake, *J. Am. Chem. Soc.* **2015**, *137*, 9481.  
b) C. A. Malapit, I. K. Luvaga, J. T. Reeves, I. Volchkov, C. A. Busacca, A. R. Howell, C. H. Senanayake, *J. Org. Chem.* **2017**, *82*, 4993.
- 17) K. Ninomiya, T. Shioiri, S. Yamada, *Tetrahedron* **1974**, *30*, 2151.
- 18) T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203.
- 19) M. Kitamura, M. Yano, N. Tashiro, S. Miyagawa, M. Sando, T. Okauchi, *Eur. J. Org. Chem.* **2011**, 458.
- 20) M. Kitamura, N. Tashiro, S. Miyagawa, T. Okauchi, *Synthesis* **2011**, 1037.
- 21) A. Mishra, S. Batra, *Curr. Top. Med. Chem.* **2013**, *13*, 2011.
- 22) M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *Tetrahedron Lett.* **1993**, *34*, 3389.
- 23) Y. Ma, G. A. O'Doherty, *Org. Lett.* **2015**, *17*, 5280.
- 24) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.
- 25) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.
- 26) Review: P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12654.
- 27) K. Liu, S. Tang, T. Wu, S. Wang, M. Zou, H. Cong, A. Lei, *Nat. Commun.* **2019**, *10*, 639.

## Reagents for Amination

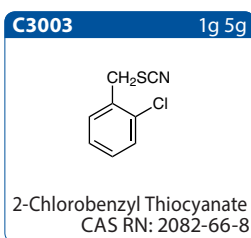
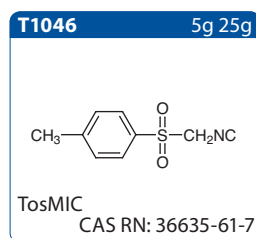
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		<b>B2303</b> 1g 5g 25g  <i>N</i> -Boc-2-nitrobenzenesulfonamide CAS RN: 198572-71-3	<b>C1757</b> 5g 25g  <i>N</i> -Cbz-2-nitrobenzenesulfonamide CAS RN: 245365-64-4	<b>A1632</b> 5g  <i>N</i> -Alloc-2-nitrobenzenesulfonamide CAS RN: 90916-29-3	<b>A1441</b> 5g 25g  Acetoxime <i>O</i> -(2,4,6-Trimethylphenylsulfonate) CAS RN: 81549-07-7	<b>H0530</b> 25g 100g 500g  Hydroxylamine- <i>O</i> -sulfonic Acid CAS RN: 2950-43-8
		<b>D2479</b> 25g  Sodium Diformylamide CAS RN: 18197-26-7	<b>B1734</b> 5g  <i>N</i> -Boc-phosphoramidic Acid Diethyl Ester CAS RN: 85232-02-6	<b>I0497</b> 5g 25g  Di- <i>tert</i> -butyl Iminodicarboxylate CAS RN: 51779-32-9	<b>B2857</b> 1g 5g  <i>tert</i> -Butyl [Bis(4-methoxyphenyl)-phosphinyloxy]carbamate CAS RN: 619333-95-8	<b>B1648</b> 10g 25g  <i>N</i> -Boc- <i>p</i> -toluenesulfonamide CAS RN: 18303-04-3
		<b>A1341</b> 5g  Azidomethyl Phenyl Sulfide CAS RN: 77422-70-9	<b>A1137</b> 25g 250g  4-Amino-1,2,4-triazole CAS RN: 584-13-4			

## Reagents for Nitration

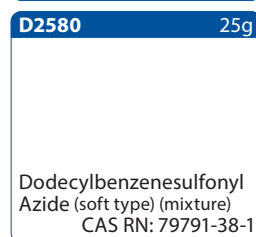
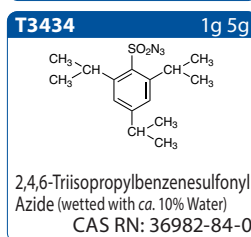
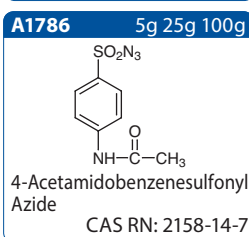
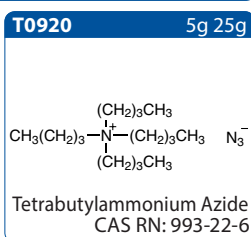
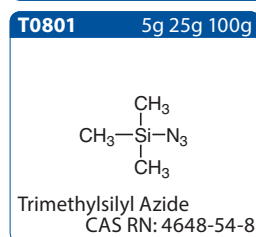
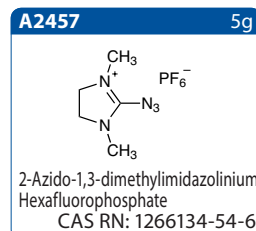
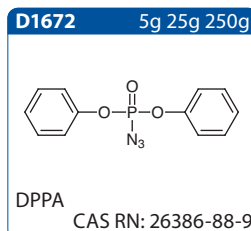
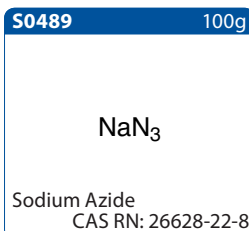
<b>Reagents for Nitration</b>		<b>T1431</b> 5g 25g  2,3,5,6-Tetrabromo-4-methyl-4-nitro-2,5-cyclohexadien-1-one CAS RN: 95111-49-2	<b>N0806</b> 300mL HNO <sub>3</sub> Nitric Acid (67%) CAS RN: 7697-37-2	<b>U0015</b> 25g  Urea Nitrate (wetted with ca. 25% Water) CAS RN: 124-47-0		
		<b>G0164</b> 25g  Guanidine Nitrate CAS RN: 506-93-4	<b>T3082</b> 5g 25g  Tetraethylammonium Nitrate CAS RN: 1941-26-0	<b>T3651</b> 5g 25g  Tetrabutylammonium Nitrate CAS RN: 1941-27-1		
		<b>Reagents for Cyanation</b>		<b>T0198</b> 25g 500g  Benzyl Thiocyanate CAS RN: 3012-37-1	<b>C0441</b> 25g 500g  Ethyl Cyanoacetate CAS RN: 105-56-6	<b>B1274</b> 5mL 25mL  <i>tert</i> -Butyl Isocyanide CAS RN: 7188-38-7
				<b>D5514</b> 5g 25g  Dimethylmalononitrile CAS RN: 7321-55-3	<b>C1952</b> 25g 300g CuCN Copper(I) Cyanide CAS RN: 544-92-3	<b>T0990</b> 25mL 100mL 500mL  Trimethylsilyl Cyanide CAS RN: 7677-24-9

## Reagents for Cyanation

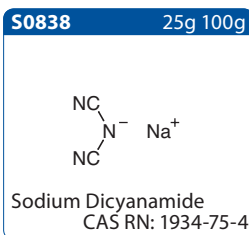
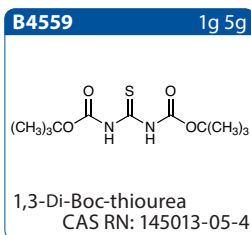
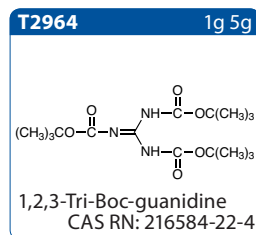
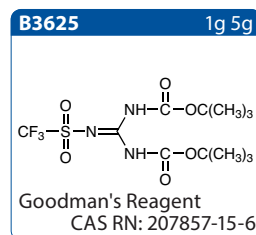
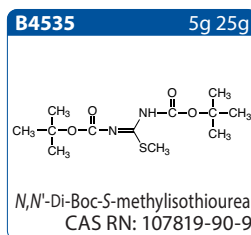
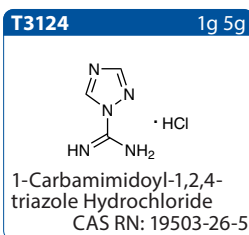
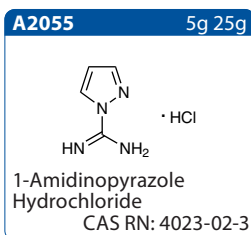
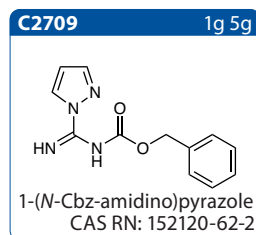
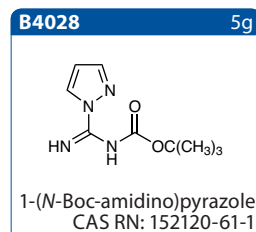
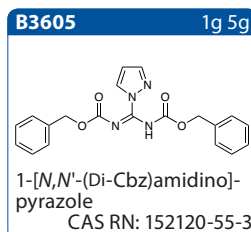
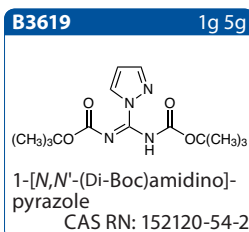
## C-N Bond Formation Reactions



### Reagents for Azidation and Diazotization



### Reagents for Guanidinylation



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