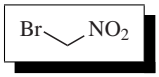
Bromonitromethane



[563-70-2] CH_2BrNO_2 (MW 139.94)
InChI = 1S/CH2BrNO2/c2-1-3(4)5/h1H2
InChIKey = DNPRVXJGNANVCZ-UHFFFAOYSA-N

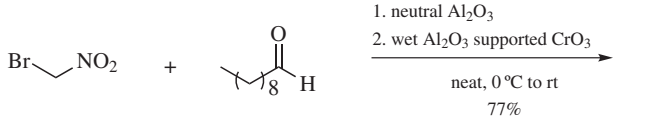
(reagent used as both nucleophile and electrophile, and for the synthesis of the pharmaceutically important cyclic compounds)

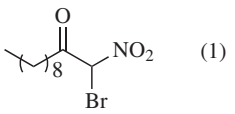
Physical Data: mp −28°C; bp 146–148°C/750 mmHg; *d* 2.007 g cm^{-3}; Fp 113 °C.
Solubility: sol toluene, ether, and most organic solvents.
Form Supplied in: yellow liquid; widely available.
Purification: purified by distilling (40–52°C/16 mmHg).
Handling, Storage, and Precautions: keep container tightly closed. Keep container in a cool, well-ventilated area. Separate from acids, bases, reducing reagents and combustibles. Empty containers pose a fire risk, evaporate the residue under a fume hood. Do not ingest. Avoid contact with skin and eyes.

Original Commentary

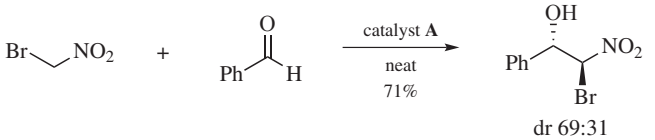
Tsubasa Inokuma & Yoshiji Takemoto
Kyoto University, Kyoto, Japan

1,2-Additions. Due to the acidity of the α-proton ($p_{Ka} = 12.5 \pm 0.1$ in DMSO)[1] of bromonitromethane, this reagent serves as a nucleophile in the presence of proper additives. Aldehydes and azetidine-2,3-diones can be used as electrophilic partners (eqs 1–5).[2] When the substrate has chiral centers, high diastereoselectivity is obtained in some cases. In the presence of a copper catalyst and chiral ligands, good enantioselectivity can be achieved in this reaction. Although the diastereoselectivity is low, the bromo group can be easily removed under radical conditions.

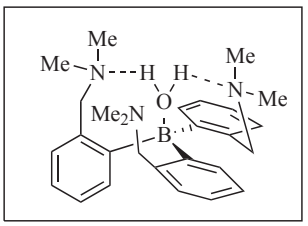




(1)

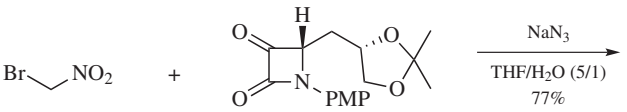


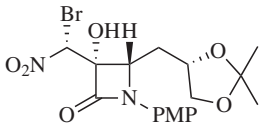
dr 69:31



(2)

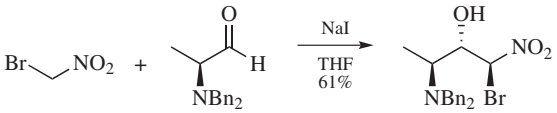
catalyst **A**





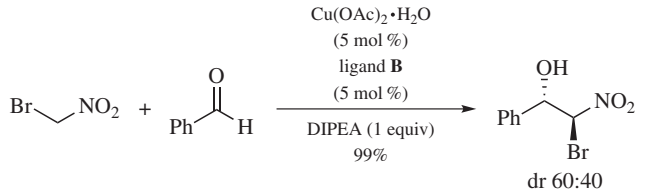
(3)

dr 85:15

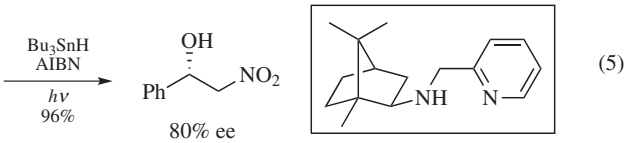


(4)

dr 98.5:2.5



dr 60:40

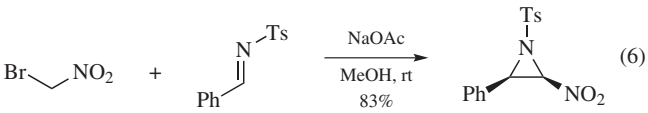


80% ee

(5)

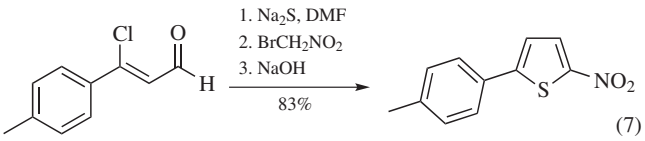
ligand **B**

In addition, the resulting bromoalkane derivatives have an electrophilic nature, so they are suitable substrates for the synthesis of some fascinating heterocyclic compounds. Until now, aziridines, thiophenes, furopyrimidinones, and 4,5,6,7-tetrahydrothieno [3,2,c]pyridines have been synthesized by this procedure (eqs 6–9).[3]



(6)

dr 92:8



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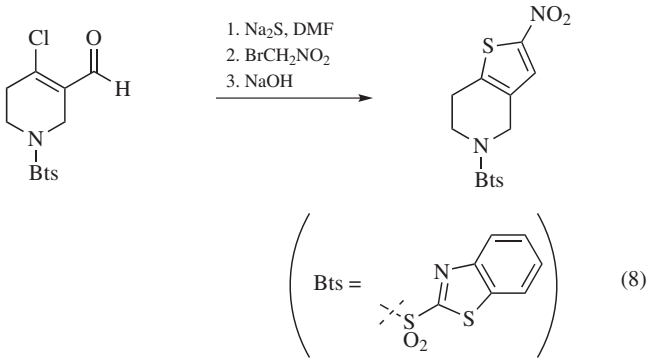

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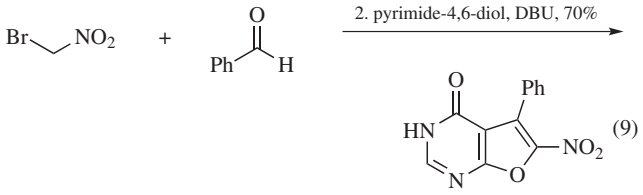
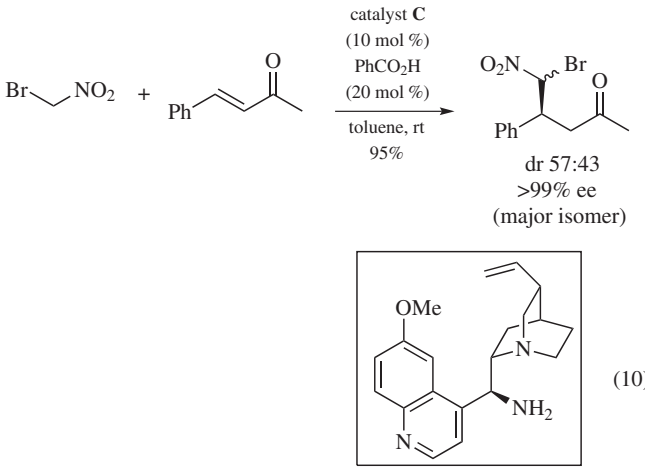


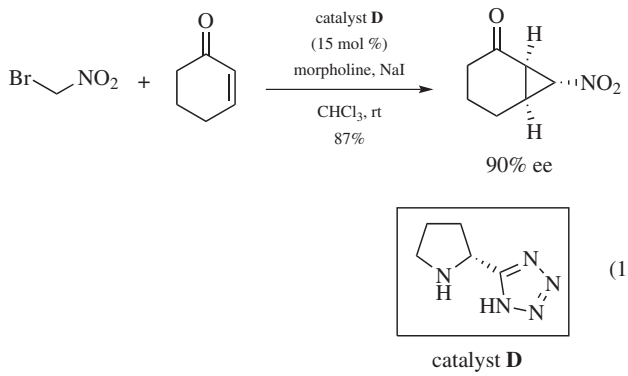
(9)

1,4-Additions. There are several reports of 1,4-additions of bromonitromethane to a variety of electrophiles such as enones, enals, and α,β-unsaturated α-cyanoimides (eqs 10–15).[4] Different from 1,2-addition, several asymmetric catalytic 1,4-additions have already been reported. Chiral amines, pyrrolidines, and aminothioureas can be used as asymmetric catalysts in these reactions. The products are useful precursors for the synthesis of nitrocyclopropanes under basic conditions. However, there are still problems with low diastereoselectivities when acyclic compounds are used as substrates.



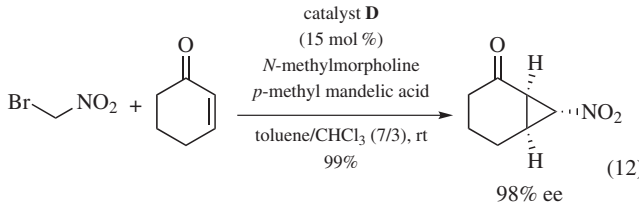
(10)

catalyst **C**

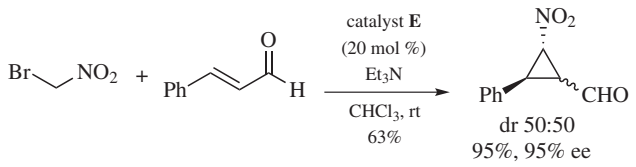


(11)

catalyst **D**

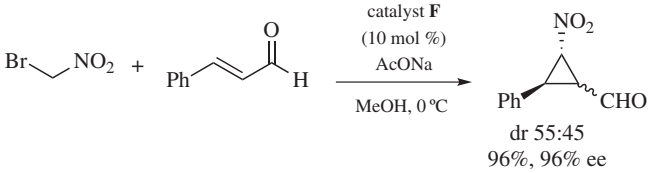


(12)



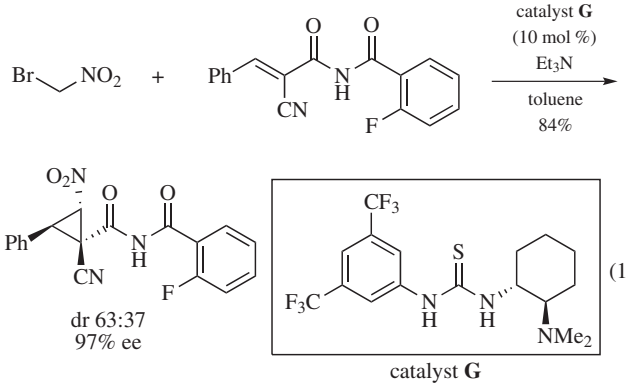
(13)

catalyst **E**



(14)

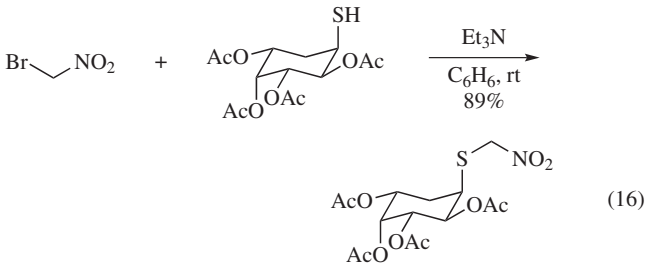
catalyst **F**



(15)

catalyst **G**

Electrophilic substitutions. Several nucleophiles such as thiolates and alkyllithium compounds react with bromonitromethane to give the corresponding nitroalkane derivatives (eqs 16–18).[5] The products can subsequently be used as nucleophiles for further transformations.



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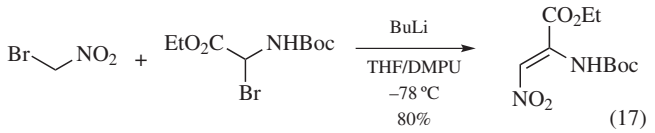

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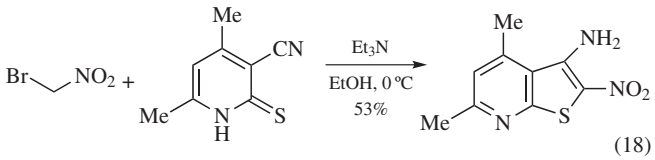
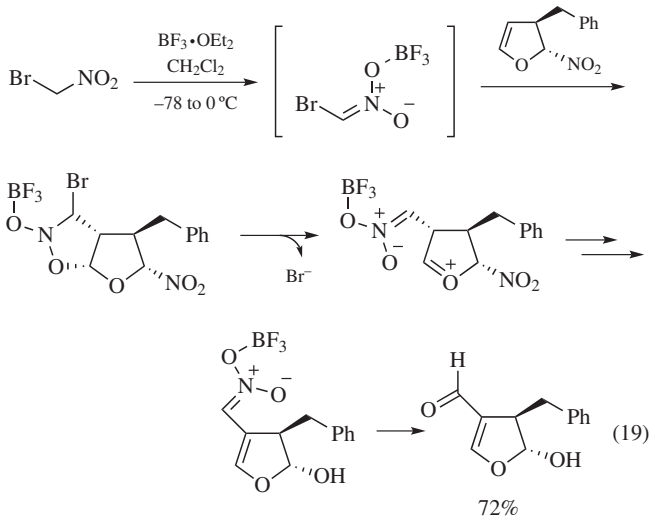


(18)

1,3-Dipolar cycloadditions. When bromonitromethane is treated with Lewis acids, the corresponding 1,3-dipole is generated and it can be used as substrate for 1,3-dipolar cycloadditions. However, examples of these reactions are quite limited until now.

$BF_3 \cdot OEt_2$ can be used as a Lewis acid for generating the 1,3-dipole (eq 19)[6]. The reaction sequence consists of a [3+2] cycloaddition with dihydrofuran, fragmentation of the heterobicyclic compound, intramolecular cyclization, ring opening reaction, and a Nef reaction of the resultant nitronate compound.

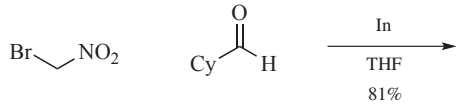


(19)

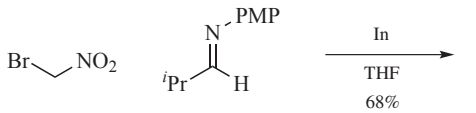
First Update

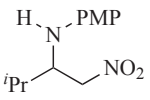
Sergey V. Tsukanov & Jeffrey N. Johnston
Vanderbilt University, Nashville, TN, USA

Barbier-type Additions to Aldehydes and Imines. Reductive procedures using indium or samarium metals have been reported as alternatives to the usual generation of nitronate by deprotonation under basic conditions (eqs 20–24).[7] In these cases, bromonitromethane is a functional equivalent to nitromethane, and amino alcohols and nitroamines are prepared under mild conditions and with a broad scope of substrates. The ability to prepare products with aliphatic (enolizable) aldehydes and imines is notable. These conditions were also successfully applied toward more complex carbohydrates to furnish a variety of nitro and amino sugars with moderate diastereoselectivity and in good yield (eq 24).

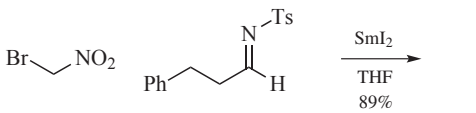


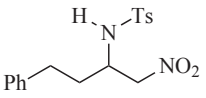
(20)





(21)





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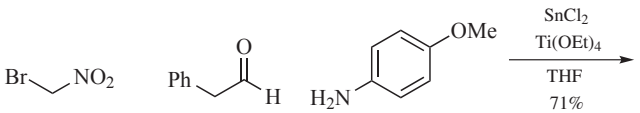
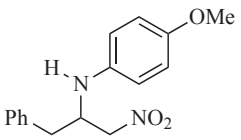
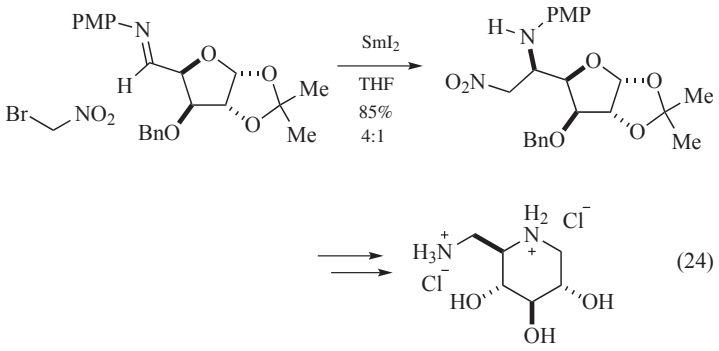




(23)

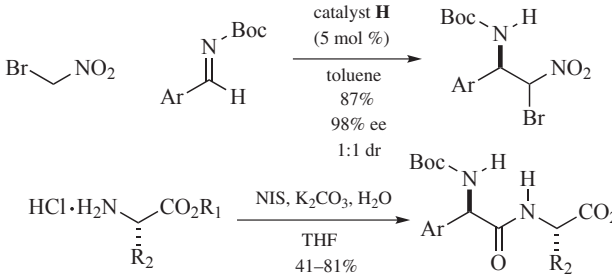
Chiral Bromonitroalkanes as Precursors to Natural and Nonnatural Amino Acids. The discovery of umpolung amide synthesis (UmAS)[8] has further improved the utility of bromonitromethane as a reagent and has enhanced its synthetic impact. These developments have largely highlighted the advantage of amide formation using a unique mechanism wherein the



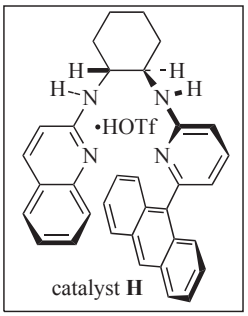
(24)

6-amino-1,6-dideoxynojirimycin

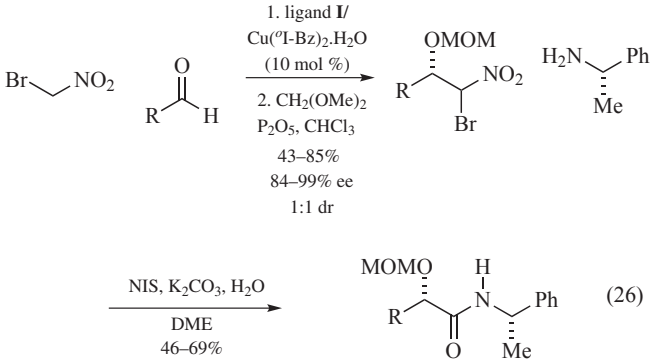
carbon and nitrogen polarities are reversed (umpolung) at the carbon–nitrogen bond-forming stage.[9] Several methods to prepare enantioenriched chiral α-bromonitroalkane donors have been reported (eqs 25–28),[10,11] and UmAS allows these donors to function as surrogates for chiral α-hydroxy carboxylic acids (eq 26) and aryl glycine α-amino acids (eq 25). Bromonitromethane behaves like nitromethane in BAM-catalyzed additions to *N*-Boc imines,[12] but the bromine-substituted carbon is typically produced as a mixture of epimers. This feature is of little consequence since the bromine-substituted carbon becomes the sp^2-hybridized carbon of the amide product resulting from UmAS. The scope of substrates is broad and most aromatic aldimines provide the amide precursors in high yields and with excellent enantioselectivity. A diverse group of *N*-protecting groups can now be accessed by the addition of bromonitromethane to trimethylsilyl imines (eq 27).[10] Natural amino acids can participate in UmAS coupling reactions with α-bromonitroalkanes to provide peptidic products (protecting groups are required for certain side chain functionalities),[8] and amide bond formation substoichiometric in NIS is effective using oxygen as a terminal oxidant.[13] Finally, it was reported that the addition products of bromonitromethane can be converted to their corresponding diamines by a cobalt-mediated reduction providing a high-yielding and an efficient alternative to a direct nitromethane addition in challenging cases (eq 28).[14]



Ar = $^{p}ClC_6H_4$; R^1 = Me, Et, or ^{t}Bu
Amino acids: Gly, Ala, Val, Leu, Ile, Ser, Thr
Phe, Tyr($O^{t}Bu$), Asp(CO_2Me), Asn, Glu(CO_2Et)
Gln, Lys(NHCbz), Pro, Cys(SBn), Met, His(NTr)
Arg(N-NO_2), Tyr(NBoc)

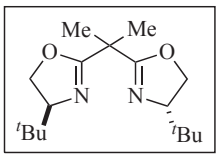


(25)

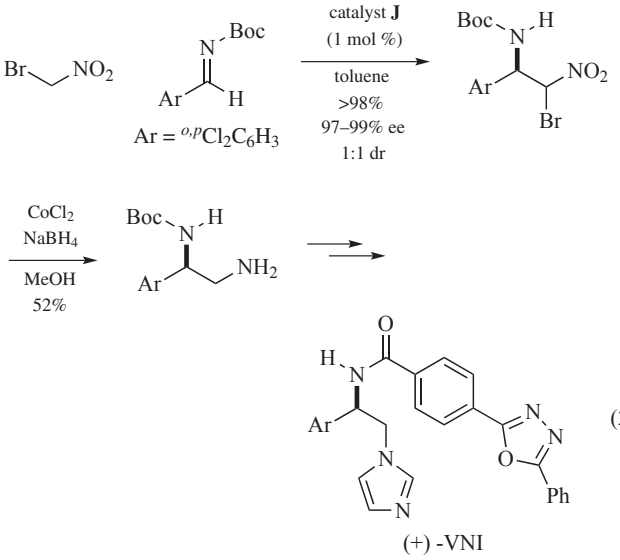


(26)

R = C_6H_5, $^{p}MeC_6H_4$, $^{p}PhC_6H_4$, $^{p}MeSC_6H_4$ $^{p}MeOC_6H_4$, $^{p}FC_6H_4$, $^{p}CF_3C_6H_4$ $^{m}BrC_6H_4$ $^{m}MeOC_6H_4$, $^{o}MeOC_6H_4$ $^{o}BrC_6H_4$ $^{o}MeC_6H_4$ $^{o}MOMOC_6H_4$, *N*-Ts-^{2}indole, *N*-Ts-^{2}pyrrole C_6H_{11}, $PhCH_2CH_2$ ^{3}thiophene

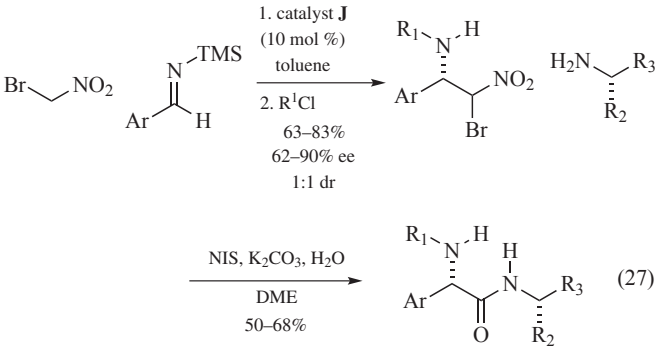


ligand **I**



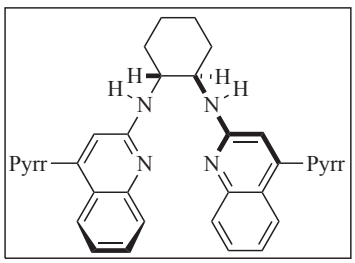
(28)

(+) -VNI



(27)

R^1 = Ac, Bz, Fmoc, Piv, N_3Ac, Cbz, Alloc
Ar = C_6H_5, $^{p}MeOC_6H_4$, $^{p}CF_3C_6H_4$, $^{p}IC_6H_4$ $^{m}ClC_6H_4$, $^{p}BrC_6H_4$, $^{p}FC_6H_4$, $^{o,p}Cl_2C_6H_3$, $^{p}MeC_6H_4$
R_2 = Me, R_3 = Ph; R_2 = ^{i}Bu, R_3 = $CO_2{}^{t}$Bu
R_2 = Me, R_3 = CO_2Me



catalyst **J**

1. Bordwell, F. G.; Bartmess, J. E.; *J. Org. Chem*. **1978**, *43*, 3101.
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