“Batch and Continuous-Flow One-Pot Processes using Amine Diazotization to Produce Silylated Diazo Reagents”

Audubert, C.; Gamboa Marin, O. J.; Lebel, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 6294 –6297.

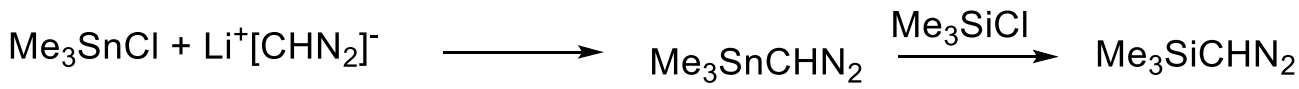
Leila Terrab

Wipf Group

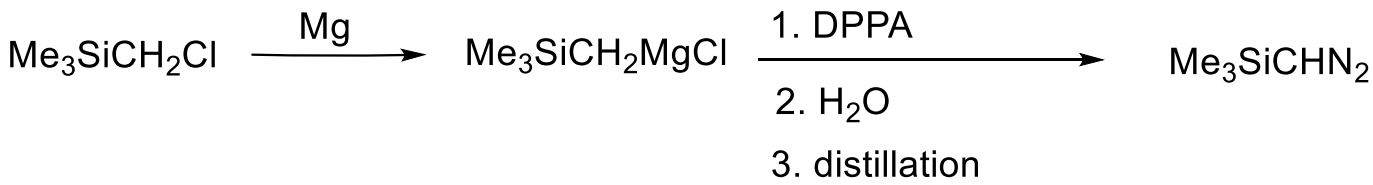
06/10/2017

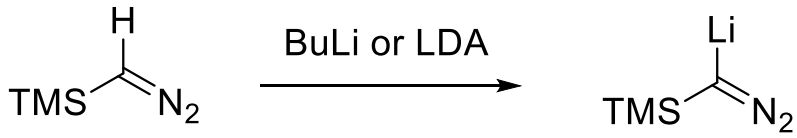
Trimethylsilyldiazomethane

Lappert- First report of covalent organometallic diazoalkanes:



Shioiri and Aoyama:





Lappert, M. F.; Lorberth, J. *Chem. Comm.* **1967**, *16*, 836–837.

Shioiri, T. ; Aoyama, T. ; Snowden, T. *Encyclopedia of Reagents for Organic Synthesis* **2001**. DOI:10.1002/047084289X.rt298

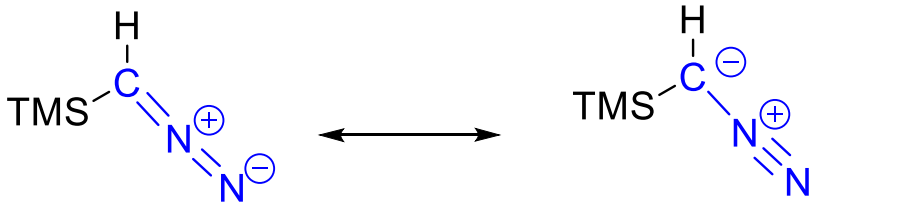
Podlech, J. *J. Prakt. Chem*. **1998**, *340*, 679.

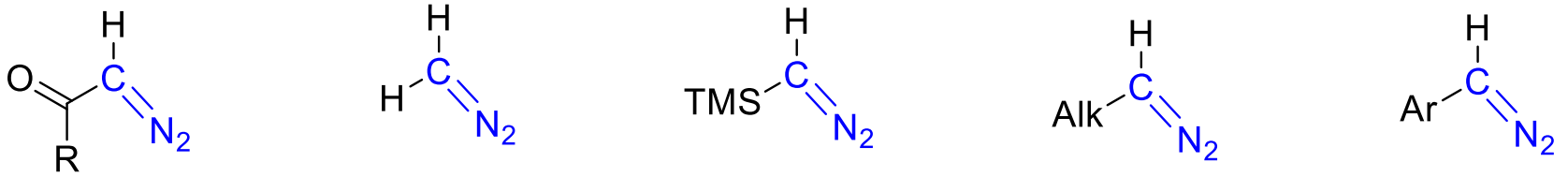
Arndt-Eistert Homologation

$TMSCHN_2$, Proposed by Aoyama and Shioiri as an alternative to diazomethane

Seyferth:

$TMSCHN_2$is known to be thermally stable due to the C-Si $p_\pi - d_\pi$ resonance:





2100-2087 | 2074 | 2070 | 2049-2020 | 2049-2020

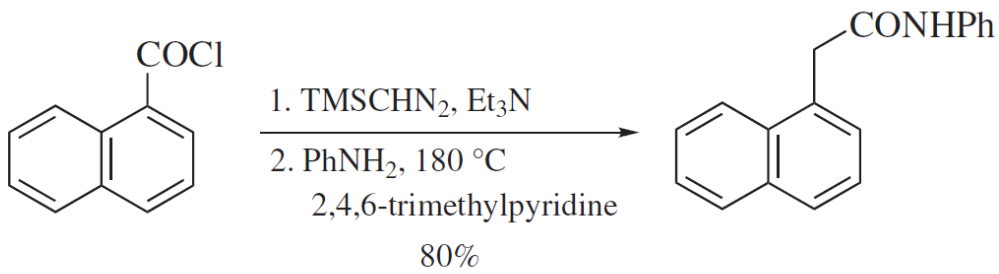
IR stretching (cm^{-1})

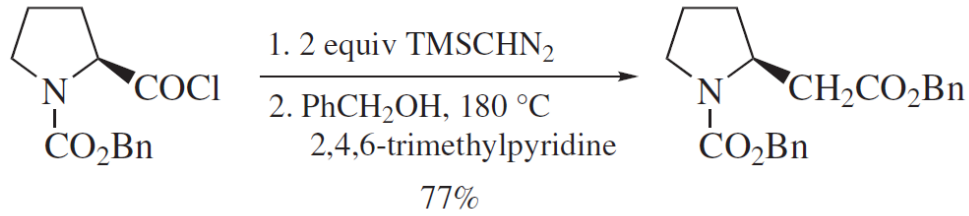
Aoyama, T.; Shioiri, T. *Tetrahedron Lett*. **1980**, *21*, 4461.

Seyferth, D.; Menzel, A. ; Dow, A. W.; Flood, T. C. *J. Organomet. Chem*. **1972**, *44*, 279.

Reactions with Trimethylsilyldiazomethane

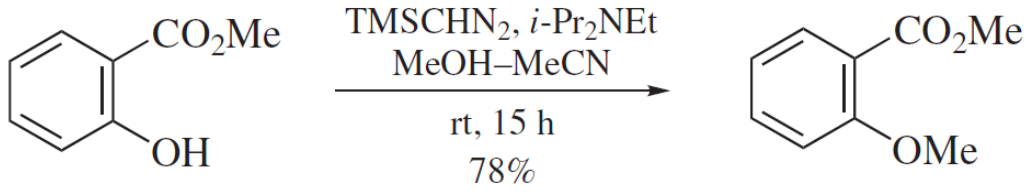
Arndt-Eistert Homologation:

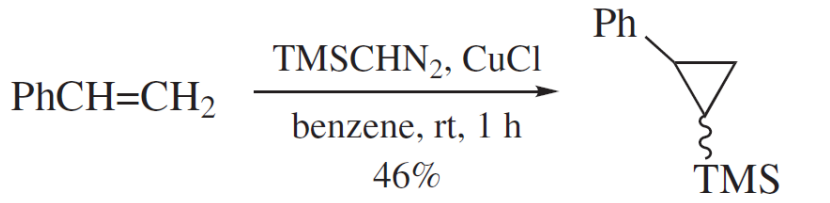




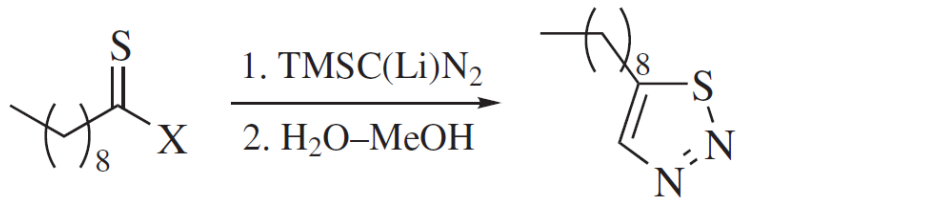
Shioiri, T. ; Aoyama, T. ; Snowden, T. *Encyclopedia of Reagents for Organic Synthesis* **2001**.

Reactions with Trimethylsilyldiazomethane





(E):*(Z)* = 1:4.8

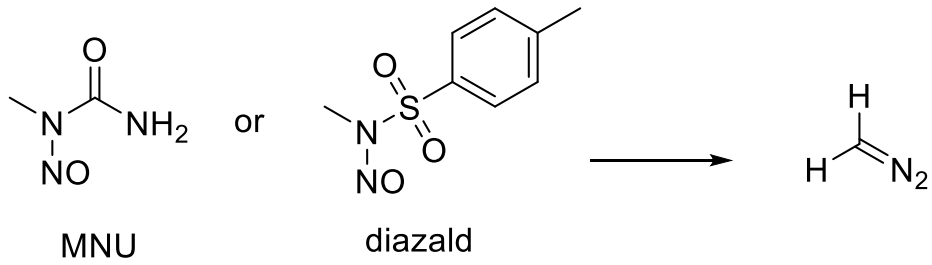


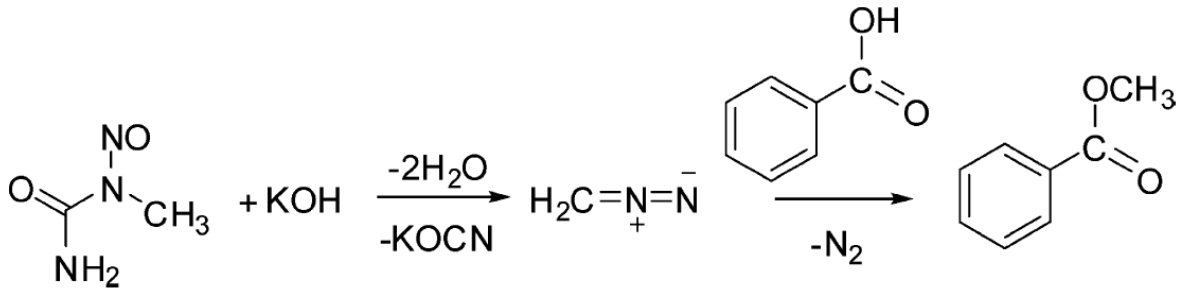
X = OMe or SMe X = OMe, 79%; SMe, 84%

Shioiri, T. ; Aoyama, T. ; Snowden, T. *Encyclopedia of Reagents for Organic Synthesis* **2001**.

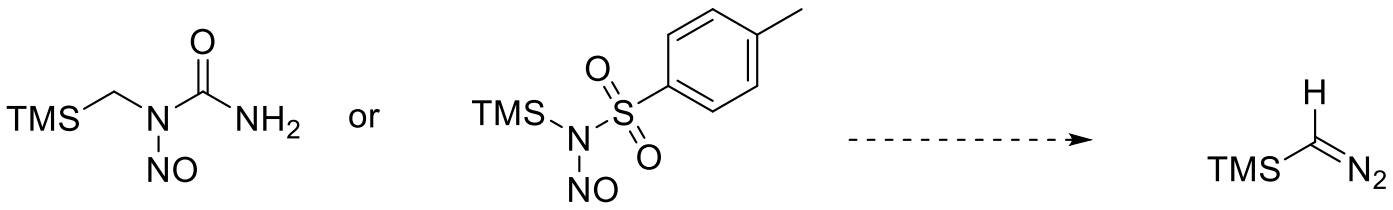
Possible Strategies to Synthesize $TMSCHN_2$

Previously reported, done by flow chemistry:





Trimethylsilylazide derivative:

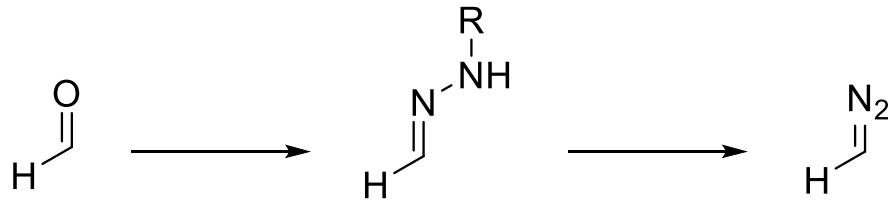


not available

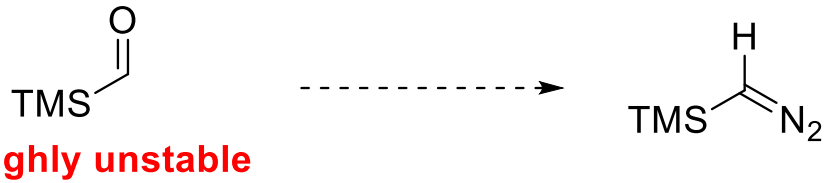
Rossi, D.; Woehl, P.; Maggini, M. *Org. Process Res. Dev.* **2012**, *16*, 1146−1149.

Possible Strategies to Synthesize $TMSCHN_2$

Diazomethane:

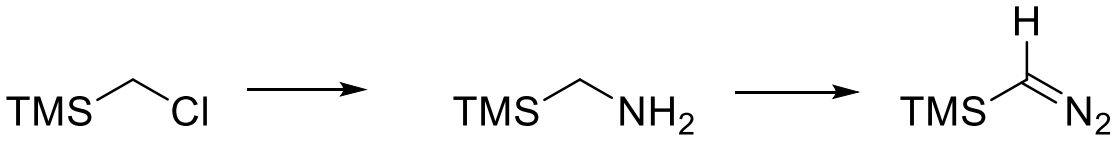


Trimethylsilylazide derivative:

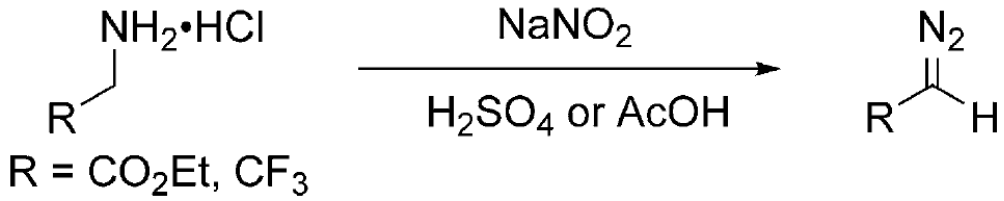


highly unstable

Synthesis used:

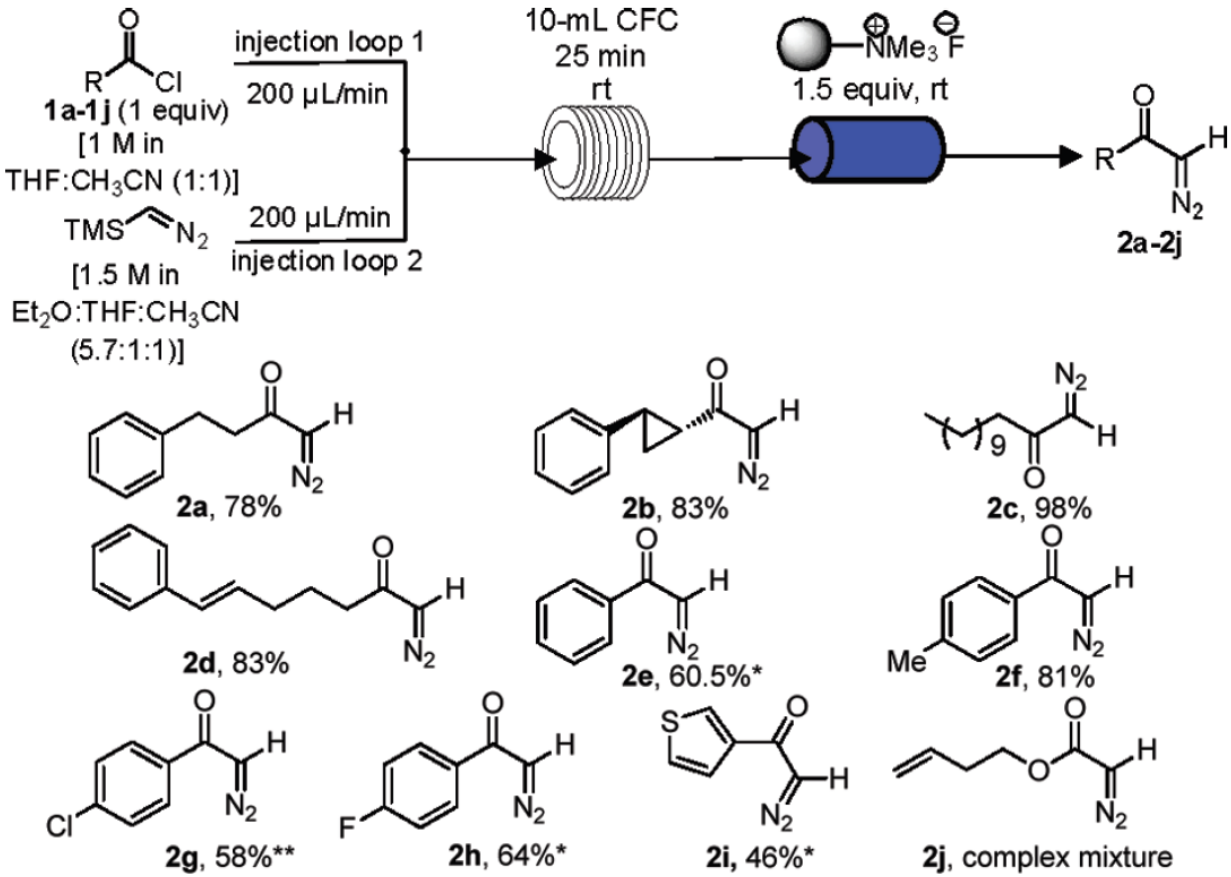


Possible strategies to synthesize $TMSCHN_2$



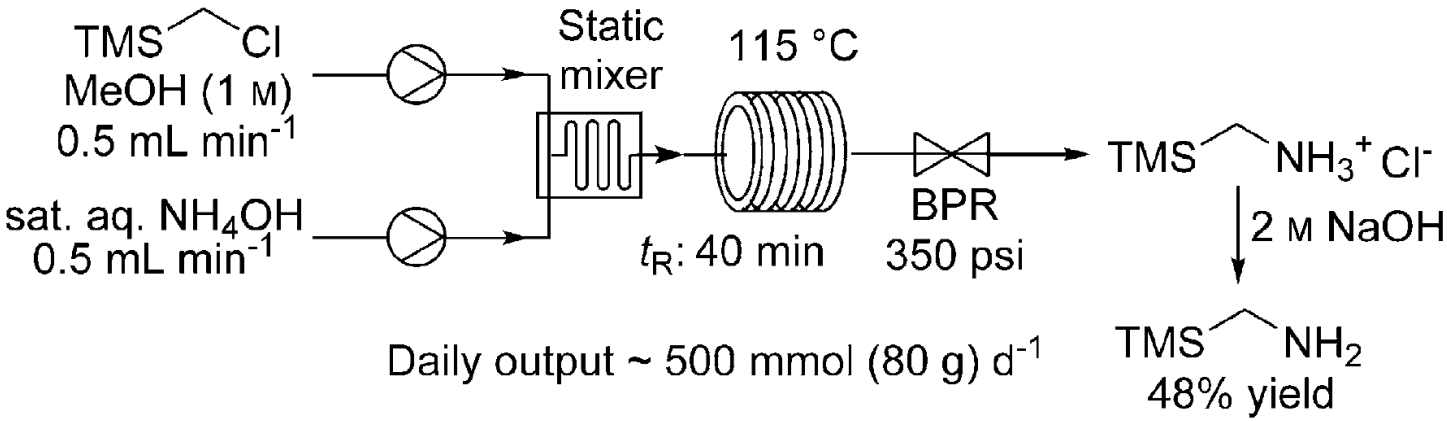
Continuous flow of trimethylsilylazide has not been reported

Scheme 2. Flow Synthesis of Diazoketones[a]



Martin, J. *et al. Org. Lett.* **2011**, 13, 320.

Flow Synthesis of Intermediate



Screening of Reaction Conditions

Acid-catalyzed diazotization

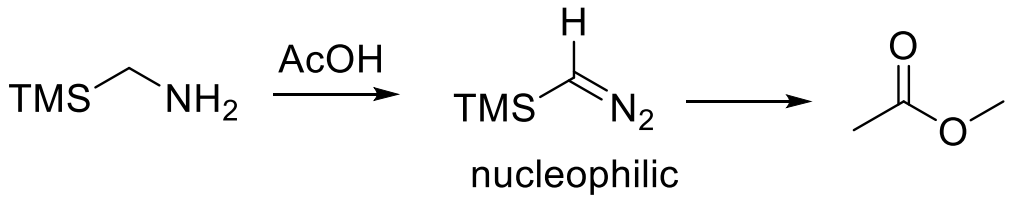
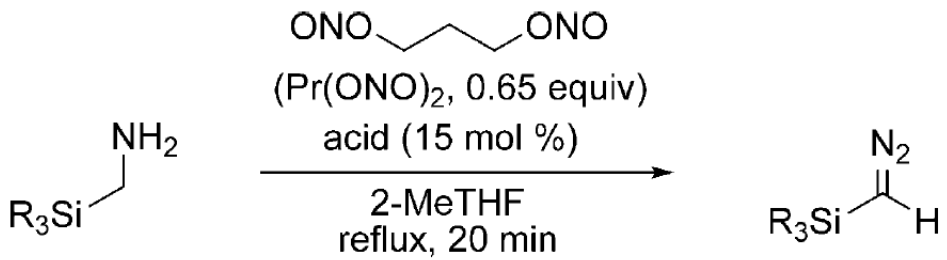


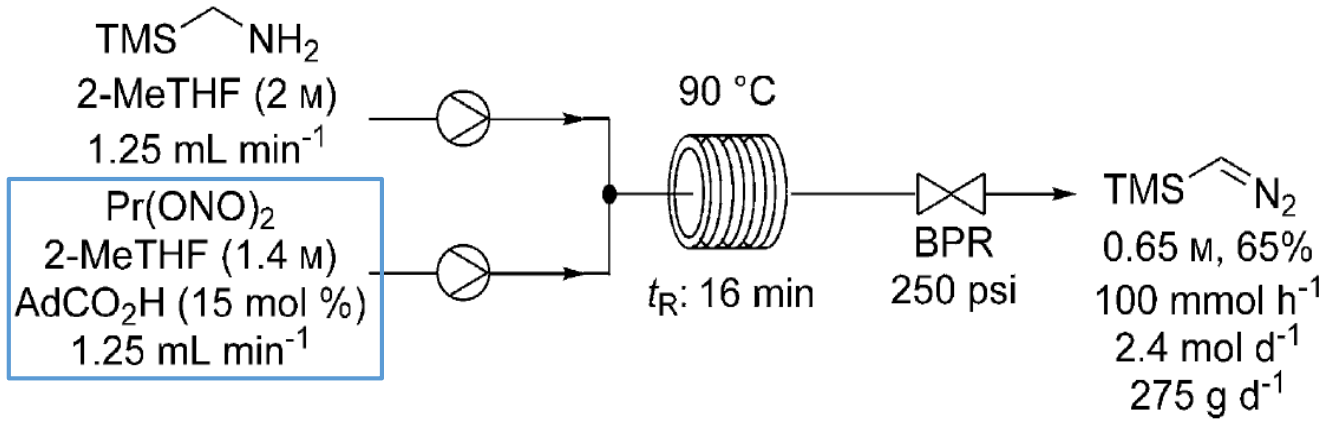
Table 1: Diazotization of $R_3SiCH_2NH_2$.



Entry	R_3Si	Acid	Yield [%][a]
1	Me_3Si	AcOH	62
2	Me_3Si	$AdCO_2H$	71
3	Me_3Si	$4\text{-}NO_2C_6H_4OH$	72
4	Me_2PhSi	$AdCO_2H$	63
5	Me_2PhSi	$4\text{-}NO_2C_6H_4OH$	77
6	$MePh_2Si$	$AdCO_2H$	73[b]
7	$MePh_2Si$	$4\text{-}NO_2C_6H_4OH$	71[c]

[a] Yield determined by ^1H NMR analysis using 1,2-diphenylethane as an internal standard. [b] Reaction time = 10 min. [c] Reaction time = 40 min. THF = tetrahydrofuran.

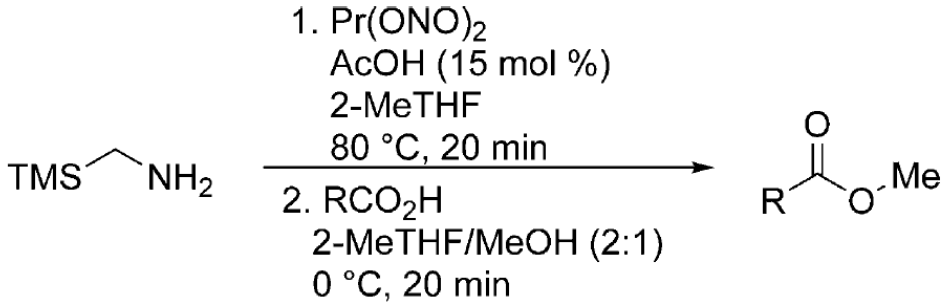
Proposed Flow Synthesis

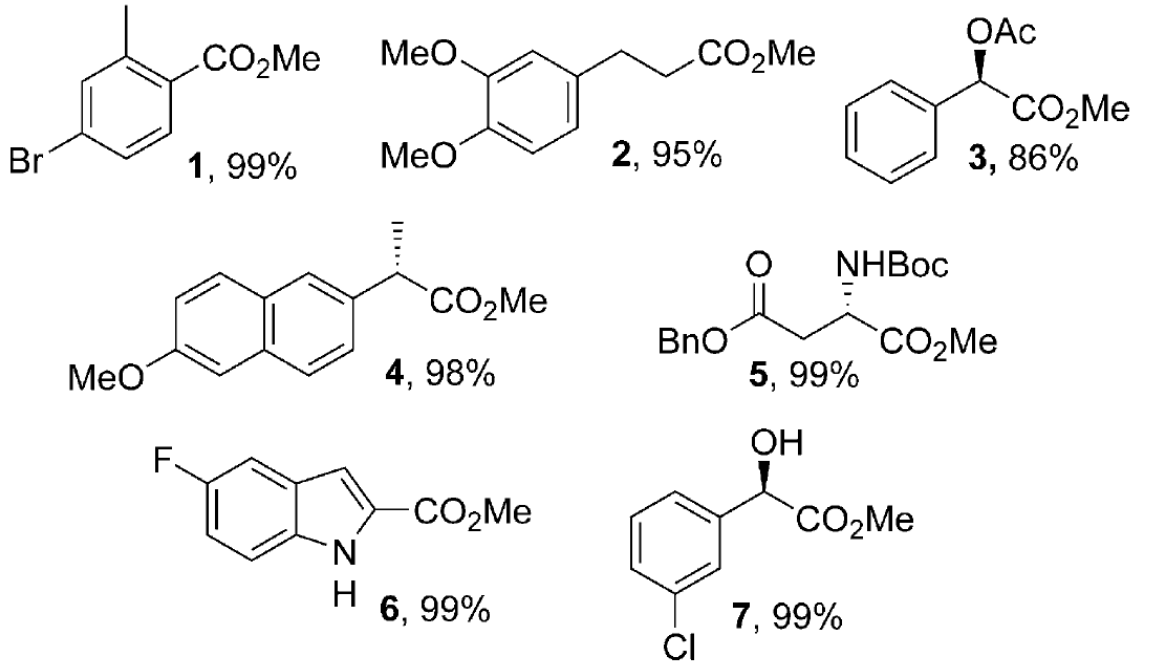


Scheme 4. Continuous-flow synthesis of $TMSCH_2N_2$.

One-pot: Synthesis of Esters

Table 2: One-pot esterification of carboxylic acids with $TMSCH_2NH_2$.[a]

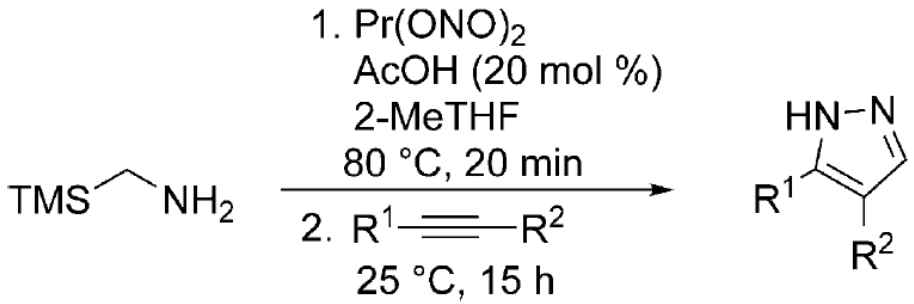


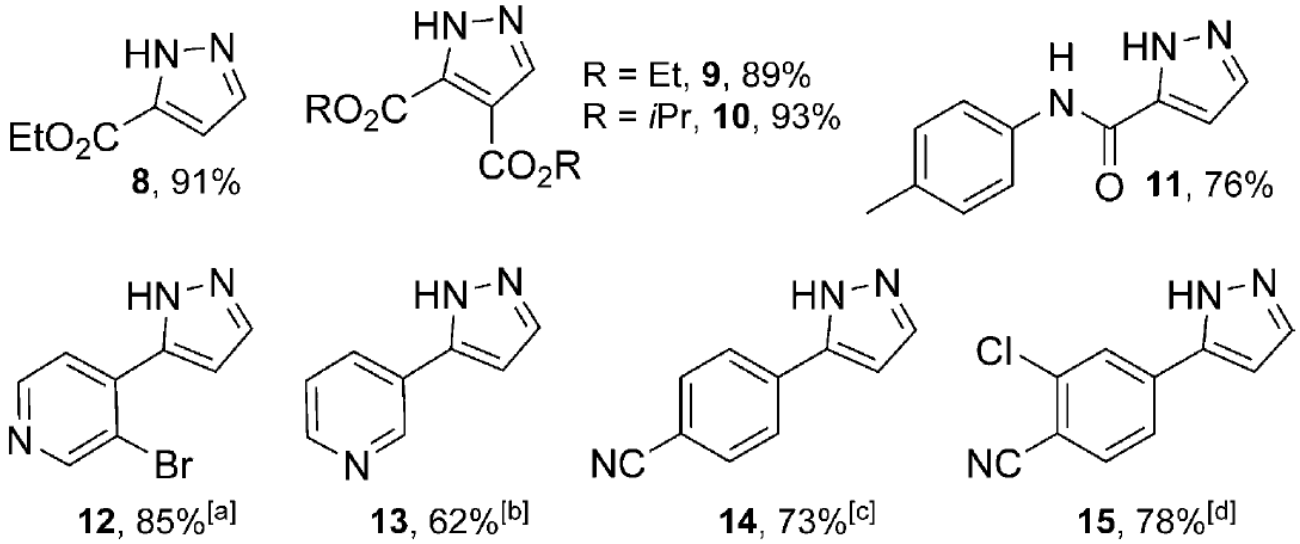


[a] Isolated yields. Boc = *tert*-butoxycarbonyl.

One-pot: Synthesis of Pyrazoles

Table 3: One-pot 1,3-dipolar cycloaddition of alkynes with $TMSCH_2NH_2$.





[a] RT, 60 h. [b] The 1,3-dipolar cycloaddition was performed in continuous flow at 100 °C for 30 min with a flow rate of 1.33 mL min^{-1}. [c] 50 °C, 36 h. [d] The 1,3-dipolar cycloaddition was performed in continuous flow at 100 °C for 15 min, then 120 °C for 15 min with a flow rate of 1.33 mL min^{-1}.

Rhodium-catalyzed methylenation

Work-up necessary for nitrite-sensitive reagents:

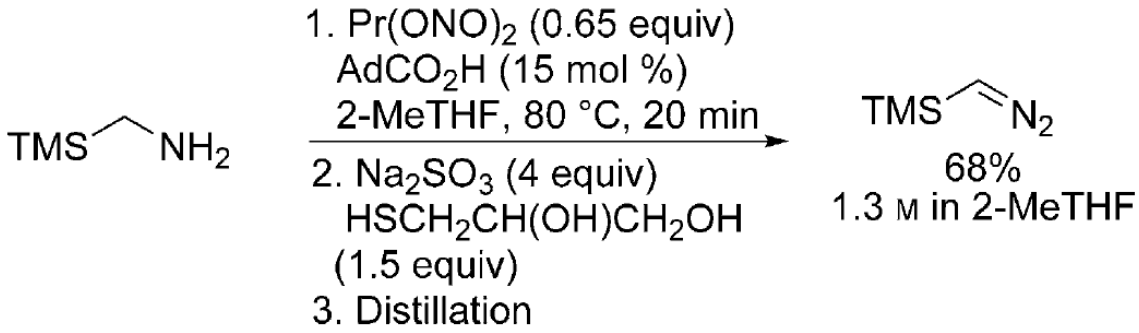
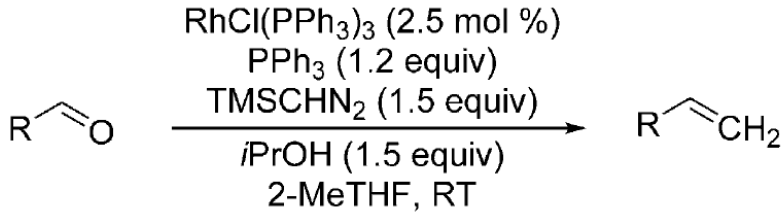
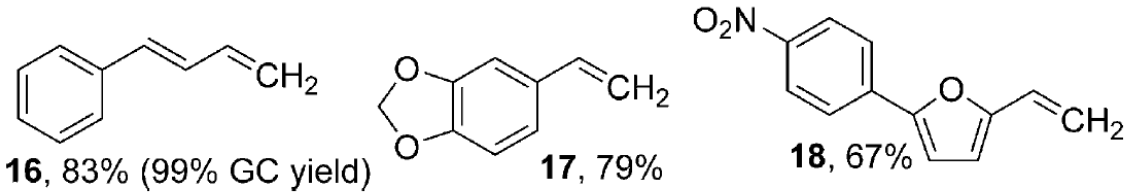


Table 4: Rhodium-catalyzed methylenation of aldehydes with $TMSCHN_2$ in 2-MeTHF.[a]

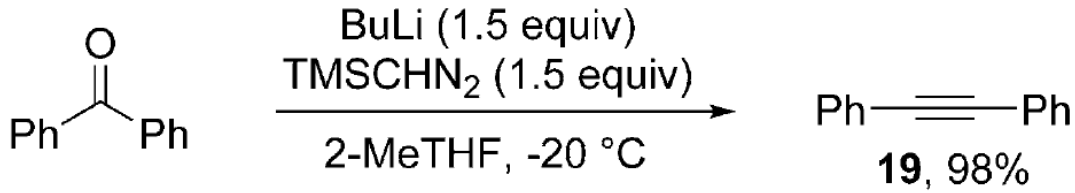




16, 83% (99% GC yield) **17**, 79% **18**, 67%

[a] Isolated yields.

Homologation of ketones



Conclusion

- Batch and flow synthesis of $TMSCHN_2$ from $TMSCH_2NH_2$ using propyldinitrite and acetic acid derivatives.

- $TMSCH_2NH_2$ used in the continuous flow reactions of carboxylic acid esterification and pyrazole formation from alkynes.

- Developed a work-up procedure of $TMSCH_2NH_2$ to be used for Rh-catalyzed methylenation and ketone homologation.