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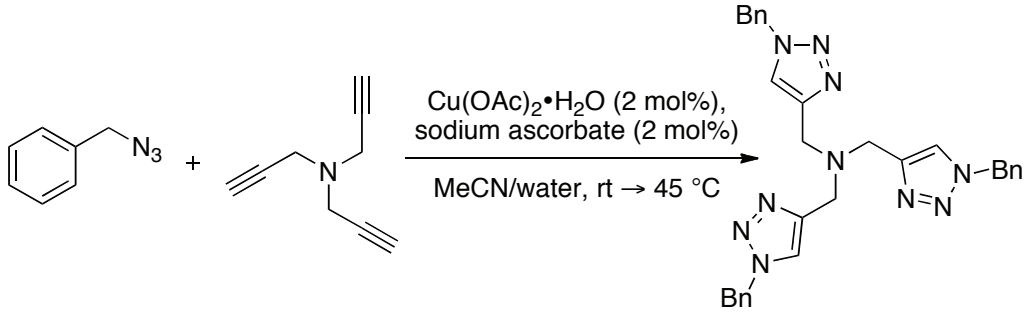
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Cu-CATALYZED AZIDE-ALKYNE CYCLOADDITION: PREPARATION OF TRIS((1-BENZYL-1*H*-1,2,3-TRIAZOLYL)METHYL)AMINE



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Checked by Jane Panteleev and Mark Lautens.[2]

1. Procedure

Caution! This procedure employs benzyl azide, which is an energetic and potentially explosive material. All transformations should be performed behind a blast shield in a well-ventilated fume hood.

Tris((1-benzyl-1H-1,2,3-triazolyl)methyl)amine. A 100-mL two-necked, round-bottomed flask equipped with a football-shaped magnetic stir bar (25 x 15 mm), condenser and thermometer (Note 1) is charged with 45 mL of MeCN (Note 2). Copper(II) acetate, monohydrate (0.0610 g, 0.305 mmol, 0.02 equiv) (Note 3) is added as a powder and the reaction mixture is stirred vigorously at room temperature until a bright blue solution is obtained. Tripropargylamine (2.00 g, 15.2 mmol, 1.00 equiv) (Note 3) and benzyl azide (3.67 g, 25.9 mmol, 1.70 equiv) are dissolved in MeCN (10 mL) (Notes 2 and 4) and added to the reaction flask, which is then immersed into a water bath. Sodium ascorbate (0.061 g, 0.31 mmol, 0.02 equiv) (Note 3) is dissolved in water (5 mL) (Note 2), and the resulting solution is added in one portion to the reaction mixture (Note 5). The reaction mixture is stirred at room temperature for 30 min (Note 6) and then heated at 45 °C (internal temperature) for 5 h. A second portion of benzyl azide (3.67 g, 25.9 mmol, 1.70 equiv) is added, and the reaction mixture is

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heated at 45 °C for an additional 19 h (Notes 7 and 8). The reaction mixture is concentrated to dryness on a rotary evaporator (40 °C, 34 mmHg). The crude residue is taken up in CH_2Cl_2 (75 mL) (Note 2) and treated with conc. NH_4OH (35 mL) (Note 3). The heterogeneous suspension is stirred vigorously on a magnetic stir plate until all solids are dissolved. The suspension is transferred to a 250-mL separatory funnel, and the aqueous layer is extracted with dichloromethane (2 × 35 mL) (Note 2). The combined organic extracts are washed with a solution of conc. aq. NH_4OH and brine (1:1 v/v, 2×15 mL) (Notes 3 and 9), dried over $MgSO_4$ (7 g) (Note 3) and filtered into a 250-mL round-bottomed flask. This solution is concentrated on a rotary evaporator (35 °C, 34 mmHg) to give a crude yellow solid. An egg-shaped Teflon-coated magnetic stir bar is added to the flask, followed by CH_2Cl_2 (50 mL) (Note 2). The suspension is vigorously stirred until a translucent, viscous solution is obtained. Diethyl ether (55 – 75 mL) (Note 2) is added gradually with vigorous stirring, causing the formation of a thick precipitate. The resulting slurry is stirred at room temperature for an additional 5 min, and the off-white precipitate is isolated by filtration (Note 10). The solid is washed with diethyl ether (3 × 15 mL) (Note 2), giving a free-flowing off-white powder (5.78 g, 10.9 mmol). The mother liquor is concentrated on a rotary evaporator, taken up in dichloromethane (25 mL) (Note 2) and precipitated with diethyl ether (50 – 75 mL) (Note 2). The precipitate is again collected by filtration and washed with diethyl ether (10 mL) (Note 2), giving a second batch of a white solid (1.0 g, 1.9 mmol). Both crops are combined to give tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine as an off-white powder (6.78 g, 12.8 mmol, 84%) (Note 11).

2. Notes

1. All glassware, stir bars and other peripheral equipment were thoroughly washed and rinsed with distilled water prior to reaction.

2. Reactions were performed with deionized water (from institutional facilities), acetonitrile (ACS reagent grade) was purchased from Sigma-Aldrich, dichloromethane (stabilized, certified ACS) was purchased from Fischer Scientific, and diethyl ether (anhydrous, stabilized, ACS reagent grade) was obtained from Caledon. The submitters purchased acetonitrile (certified ACS), dichloromethane (certified ACS) and diethyl ether (stabilized, certified ACS) from Fisher Scientific.

3. Sodium chloride (99%), anhydrous magnesium sulfate (99%) and conc. ammonium hydroxide (ACS reagent grade) were purchased from ACP Chemicals, Inc. and were used as received. The submitters purchased sodium chloride, anhydrous magnesium sulfate, conc. ammonium hydroxide (all certified ACS grade) from Fisher Scientific. Copper(II) acetate monohydrate (98%+, ACS reagent grade) and sodium ascorbate (>99%) were purchased from Sigma Aldrich. The submitters obtained copper(II) acetate monohydrate (99%) and sodium ascorbate (99%) from Acros. Tripropargylamine (98%) was purchased from GFS. Benzyl azide (94%) was purchased from Alfa Aesar and was stored away from light in a refrigerator 0–4 °C. The submitters purchased benzyl azide (99%) from Frinton Laboratories. All other materials were used as received with no other purification or special storage requirements.

4. The azide and alkyne components should be weighed out separately and sequentially dissolved into acetonitrile. The azide and alkyne reagents should not be mixed neat.

5. The solution became colorless on addition of the sodium ascorbate. The reaction solution gradually became light yellow with time and developed into a deep brown/red.

6. The submitters note that if no water bath was used, the internal temperature of the reaction gradually rose, with the maximum of 50.5 °C being observed after 30 minutes.

7. TLC analysis during the reaction allowed each of the intermediates to be visualized: (19:1 CH_2Cl_2: MeOH) tripropargylamine – R_f = 0.67, *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-*N*,*N*-dipropargyl amine – R_f = 0.38, *N*,*N*-bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-propargyl amine – R_f = 0.30, tris((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)amine R_f = 0.26. Silica gel plates – Merck (purchased from EMD chemicals), 20 x 5 cm silica gel 60 on glass, 0.25 mm coating. Samples were visualized using UV (254 nm) and $KMnO_4$ stain.

8. The submitters report a 10 h total reaction time and 75% yield. The checkers obtained a yield of 75%, but they observed incomplete consumption of reaction intermediates at 10 h reaction time. A yield of 80-84% could be obtained with a reaction time of 24 h. Addition of 0.3 equiv of benzyl azide at 24 h, and allowing the reaction to proceed for an additional 24 h further increased the yield to 92%.

9. The aqueous layer develops a bright blue color after washing with NH_4OH/brine. To ensure efficient removal of all copper salts, this color should be almost undetectable during the final wash.

10. The solid was isolated using a sintered-glass fritted funnel of medium porosity. The submitters isolated the solid using a ceramic Büchner funnel with a P4 Fisher Brand quantitative filter paper.

11. The product exhibits the following physical properties: TLC R_f = 0.26 (19:1 CH_2Cl_2: MeOH), mp = 140 °C–144 °C (the submitters report 146 °C–148 °C), IR (υ[cm^{-1}]) 3136, 3063, 3032, 2932, 2828, 1497, 1454, 1435, 1331, 1219, 1127, 1049; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (s, 6 H), 5.50 (s, 6 H), 7.23–7.28 (m, 6 H), 7.31–7.38 (m, 9 H), 7.66 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 47.05, 54.05, 123.68, 127.95, 128.62, 129.03, 134.71, 144.26; EI-MS *m/z:* 530(1, M^+), 359(30), 358(100), 187(13), 173(19), 144(10), 91(96); HRMS (EI): [M^+] calcd. for $C_{30}H_{30}N_{10}$: 530.2655. Found: 530.2662; Anal. calcd. for $C_{30}H_{30}N_{10}$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.77; H, 5.95; N, 26.52.

Safety and Waste Disposal Information

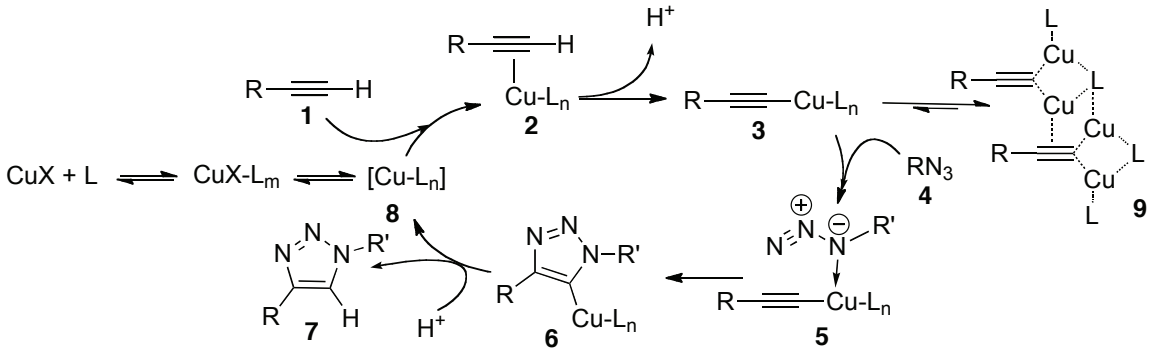
All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory": National Academy Press: Washington, DC, 1995.

3. Discussion

This procedure represents a refinement to the synthesis of the tris((triazolyl)methyl)amine family of ligands, as exemplified by the preparation of tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine. The synthesis of tris((triazolyl)methyl)amine ligands using the Cu(I)-catalyzed dipolar cycloaddition was first reported by Chan et al.[3] The general reaction proceeds via π-coordinated Cu-species **2** to give σ-copper acetylide **3** (Scheme 1). Complexation of the organic azide (**4**) via the proximal nitrogen gives coordinate complex **5**, which undergoes cycloaddition generating copper triazolide **6**. Proton transfer liberates the triazole product and regenerates free copper catalyst (**7** and **8**, respectively).[4]

In general, the rate of the cycloaddition is heavily influenced by numerous off-cycle ligated-copper species, including oligomeric copper acetylide complexes **9**.[5,6a] When poly-dentate, coordinating substrates, such

as tripropargylamine, are employed networks of extended, thermodynamically-stable oligomeric aggregates are easily formed. Thus, during the synthesis of ligands such as tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine the bulk of the copper-catalyst is tied up off-cycle, leading to a relatively slow rate of reaction. The population of monomeric (and reactive) copper acetylide can be increased by adding supportive, mono-dentate coordination ligands (aliphatic amines, 2,6-lutidine), and by employing polar-coordinating solvents (DMF, NMP, or MeCN; note that MeCN has a high affinity for Cu(I) and therefore inhibits the reaction, requiring the addition of an amine ligand and/or water). The original synthesis of the tris((triazolyl)methyl)amine ligand family used a combination of these two approaches;[3] however, we have found that omitting the supportive ligand greatly facilitates the purification and isolation of the product.



Scheme 1: Mechanism of the Cu-catalyzed azide-alkyne coupling.

Finally, running the reaction at an elevated temperature facilitates ligand exchange at the copper center, preventing the formation of thermodynamically stable, but unreactive metal complexes. However, extended heating also leads to a slow, but competitive decomposition of the azide component. To mitigate this issue benzyl azide is added to the reaction in two separate portions (2 × 1.7 equiv). This treatment obviates a large excess of the azide component and delivers the ligand in very good and reproducible yield.

The reported optimized protocol represents a practical and general method to access numerous members of the tris((triazolyl)methyl)amine ligand family (Figure 1, **10**–**14**). The efficiency of the cycloaddition permits a vast array of structurally and electronically diverse species to easily be constructed, limited only to the availability of the requisite reagent. Due to

this enormous chemical breadth, the physical and chemical properties of the ligand (solubility, polarity, steric environment, etc) can readily be tailored to specific applications.

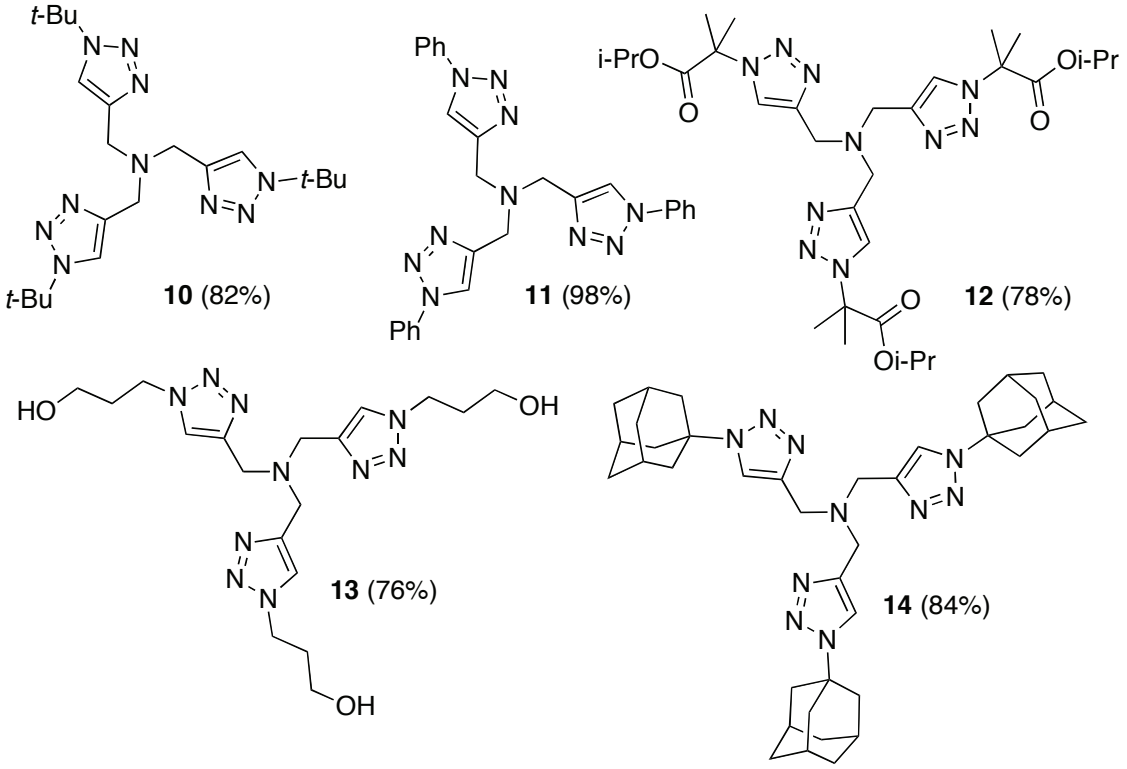


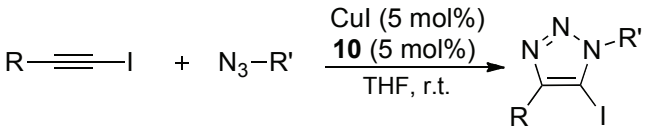
Figure 1: Various tris((triazolyl)methyl)amine ligands.

Our studies identified the tris((triazolyl)methyl))amine core as a particularly effective accelerating ligand for the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC).[3,6a] Tris((1-benzyl-1*H*-1,2,3-triazolyl)-methyl)amine (TBTA) was the first and most commonly employed CuAAC ligand; however, other related (triazolyl)methylamines including tris(1-*t*-butyl) (**10**) and tris(1-(3-hydroxypropyl)) (**13**) ligands have since been explored. These latter species have begun to supplant TBTA, as their resultant copper(I)-complexes display broader solvent compatibility while retaining high catalytic activity.

Although the most commonly employed reaction conditions for the CuAAC do not require exogenous ligands,[6] incorporating them may be advantageous when substrates displaying slow reaction profiles are used (*e.g.* low reaction concentrations, low copper loading, chelating substrates etc). Due to this feature, tris((triazolyl)methyl))amine ligands have most

often been employed in the field of bioconjugation, where very low substrate and catalyst concentrations are usually encountered.[7]

More recently, tris((triazolyl)methyl)amines have been identified as key ligands in other Cu(I)-catalyzed reactions, such as the cycloaddition between azides and 1-iodoalkynes.[8] Here, both the observed rate and chemoselectivty are strongly dependent on the nature of the ligand, with **10** being the optimal species for this process.



Scheme 2: Cu(I)-catalyzed cycloaddition between azides and 1-ioodalkynes

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Tripropargylamine: 2-Propyn-1-amine, *N*,*N*-di-2-propynyl: Tri-2-propynylamine; (6921-29-5)

Benzyl azide: (azidomethyl)benzene; (622-79-7)

Copper(II) acetate, monohydrate: Cupric acetate 1-hydrate: Acetic acid, copper(II) salt; (6046-93-1)

Sodium ascorbate: L-Ascorbic acid, sodium salt: Sodium (+)-L-ascorbate; (134-03-2)

Valery Fokin received his undergraduate education at the University of Nizhny Novgorod, Russia, and his Ph.D. degree at the University of Southern California under the tutelage of Prof. Nicos A. Petasis. After a postdoctoral stint with Prof. K. Barry Sharpless at The Scripps Research Institute in La Jolla, California, he joined the Scripps faculty, where he is currently Associate Professor in the Department of Chemistry. His research is centered on the understanding of chemical reactivity of organometallic species and on applying it to the studies of macromolecular and biological phenomena. His research group is working on new reaction development, studies of organic and organometallic mechanisms, medicinal chemistry, synthesis of macromolecular probes for imaging and drug delivery, and smart polymeric materials.

Jason Hein received his B.Sc. in biochemistry in 2000 from the University of Manitoba in Winnipeg, MB, Canada. He then began his Ph.D. studies as an NSERC postgraduate fellow under the guidance of Prof. Philip G. Hultin at the University of Manitoba. In 2005 he completed his graduate work, where he synthesized and studied a new family of soluble-supported chiral auxiliaries. He is currently an NSERC postdoctoral fellow at the Scripps Research Institute. His current interests include the design, development and study of new metal-catalyzed reactions.

After completing her undergraduate degree at the Moscow State University (M.V. Lomonosov), Moscow, Russia, Larissa Krasnova continued her graduate training at the University of Toronto under the supervision of Prof. Andrei K. Yudin. She is currently a postdoctoral associate at The Scripps Research Institute in the group of Prof. Valery V. Fokin where she carries out studies in the field of heterocyclic chemistry with an emphasis on new method development, medicinal chemistry and bioconjugation.

Masayuki Iwasaki was born in Okayama, Japan, in 1982. He obtained his B. Sc. in 2006 from Kyoto University and then began studying to receive his Ph.D. degree under the supervision of Professor Koichiro Oshima. He has been a JSPS research fellow since 2008 and is currently a visiting graduate student at the Scripps Research Institute in the group of Prof. Valery V. Fokin. His research interests include the development of new organic reactions with organometallic reagents.

Jane Panteleev received her Bachelor of Science degree in Biochemistry at Queen's University, in 2007. During this time she had the opportunity to work in the research lab of Prof. Victor Snieckus. She is currently pursuing a Ph.D. degree under the supervision of Prof. Mark Lautens at the University of Toronto. Her current research interests are in the area of asymmetric transition metal catalysis.

Tris((1-Benzyl-1H-1,2,3-Triazolyl)Methyl)Amine