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An Efficient Synthesis of Achiral and Chiral 1,2,4-Triazolium Salts: Bench Stable Precursors for N-Heterocyclic Carbenes

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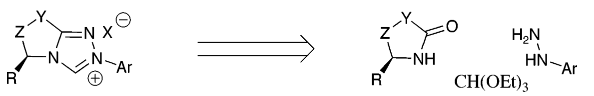


The promising utility of triazolyl N-heterocyclic carbene catalysts in umpolung aldehyde chemistry requires a straightforward reliable synthesis from readily available materials. Herein, we describe the synthesis of a variety of triazolyl N-heterocyclic carbene precursors. The reactions commence from commercially available amino acids and proceed in 44–68% overall yields. The N-heterocyclic salts are air-stable crystalline solids that can be stored with no special precaution and can generate the active catalyst when treated with an appropriate base.

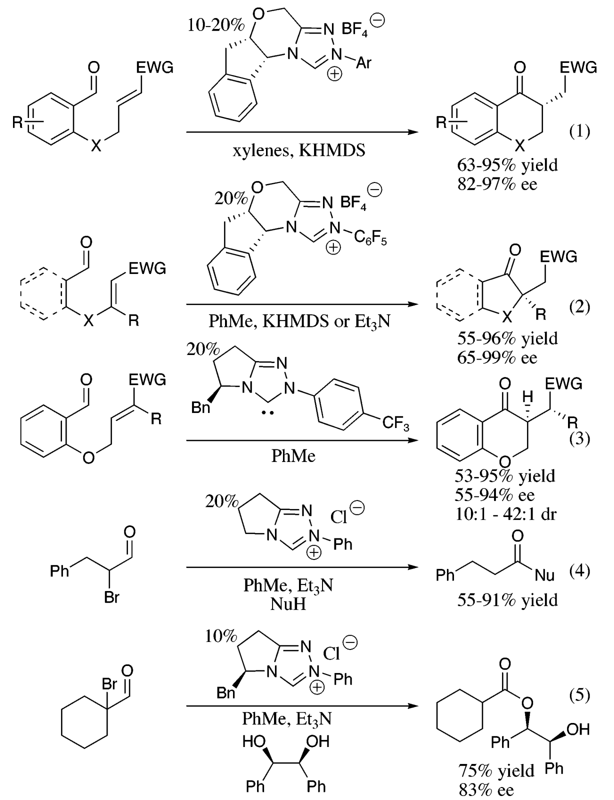
N-Heterocyclic carbenes have become a notable area of research since the first stable carbene was reported in 1991 by Arduengo and co-workers.[1] The imidazolinylidene carbene scaffold has been extensively used as a ligand in transition metal mediated processes,[2] and a number of facile procedures are available for its preparation.[3] Unlike their imidazolium salt counterparts, the preparation and utility of triazolium salts as precursors for N-heterocyclic carbenes have been less explored. Noteworthy exceptions are the practical and efficient synthesis reported by Enders and co-workers of an achiral trisphenyl-substituted triazolium salt and its transformation into the free carbene[4] and a description of the synthesis of *N*-adamantyl-substituted bisaryl triazolium salts.[5] Further reports of the syntheses of chiral bicyclic triazolium salts by Leeper[6] and Enders[7] have led to a catalyst capable of inducing high enantioselectivity in the benzoin reaction.

1 2

FIGURE 1. Chiral bicyclic triazolium salts.

In an effort to develop the utility of N-heterocyclic carbenes in asymmetric catalysis, our laboratory has pursued a practical and efficient synthesis of these triazolium salts from readily available materials. Our focus in the early stage of this research pivoted around the incorporation of easily accessible chiral building blocks into a rigid framework that could be manipulated upon further investigation. Catalyst preparation from amino acid derivatives was desirable in order to take advantage of their diverse steric profile and ready availability. Two different chiral bicyclic cores (**1** and **2**) were envisioned to possess qualities stated above (Figure 1).

We have demonstrated the utility of these triazolium salts as precursors for nucleophilic carbenes in a highly enantioselective intramolecular Stetter reaction (eq 1).[8] We have since illustrated their efficacy in the formation of quaternary stereocenters (eq 2),[9a] contiguous stereocenters (eq 3),[9b] and their application in a novel internal redox reaction manifold (eq 4) capable of generating high enantiomeric excess in a meso diol desymmetrization (eq 5).[9c] Herein, we report the synthesis of a variety of chiral and achiral triazolium salt nucleophilic carbene precursors.



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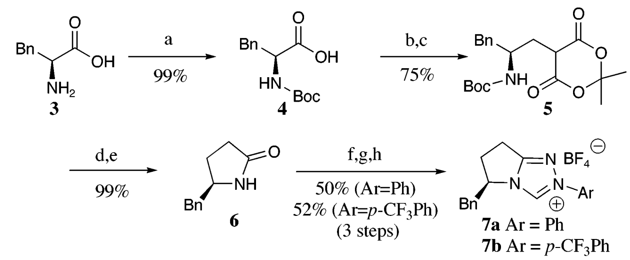
SCHEME 1. Synthesis of Pyrrolidinone-Derived Catalyst Precursors[a]



[a] (a) Boc_2O, NaOH, THF/H_2O, 23 °C; (b) Meldrum's acid, DMAP, DCC, CH_2Cl_2, 0 °C; (c) AcOH, $NaBH_4$, CH_2Cl_2, 0 °C; (d) toluene, 110 °C; (e) TFA, CH_2Cl_2, 0 °C; (f) $Me_3O{+}BF_4^-$, CH_2Cl_2, 23 °C; (g) phenylhydrazine or 4-(trifluoromethyl)phenylhydrazine, 23 °C; (h) MeOH, $CH(OMe)_3$, 80 °C or MeOH, $CH(OEt)_3$, 110 °C.

The synthesis of enantiopure bicyclic triazolium salts **7a** and **7b** began with Boc protection of phenylalanine according to Meyers' procedure (Scheme 1).[10] With an easy route to a large amount of *N*-Boc-protected phenylalanine, the synthesis of the pyrrolidinone core was realized according to literature precedent.[11] Coupling of the Boc-protected amino acid with Meldrum's acid in the presence of DMAP and DCC affords the desired product that can be used without further purification. Reduction of the ketone with slow addition of 2.5 equiv of sodium borohydride at 0 °C over 3 h followed by stirring at 0 °C for 24 h provides the desired product as yellow oil. Initial attempts at using the resulting yellow oil resulted in a complicated purification of the desired pyrrolidinone **6**. However, **5** can be recrystallized from diethyl ether, affording an analytically pure white crystalline solid. Cyclization of **5** in toluene at 110 °C followed by removal of the *N*-Boc protecting group with trifluoroacetic acid gives the desired pyrrolidinone **6** as a yellow solid that can be used without further purification.[12] With the pyrrolidinone in hand, a one-pot modification of the Leeper synthesis[6] was used for the three-step conversion into triazolium salt. Methylation of **6** with Meerwein's reagent affords the desired amidate, which was treated in situ with phenylhydrazine to generate a red solution that corresponds to the desired cyclization precursor.

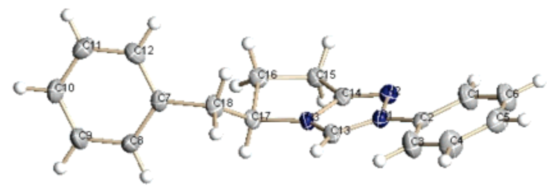
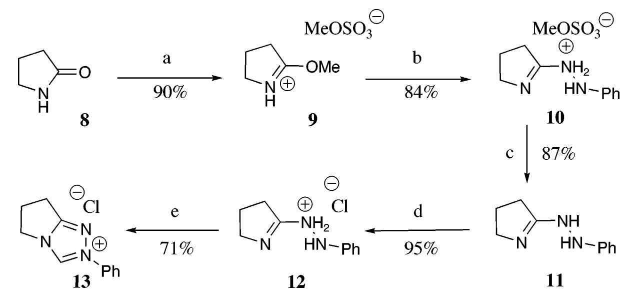


FIGURE 2. X-ray crystal structure of **7a**. Counterion and water molecule omitted for clarity.

SCHEME 2. Synthesis of Achiral Catalyst Precursor 13[a]



[a] (a) $(MeO)_2SO_2$, MeCN, 80 °C, 12 h; (b) phenylhydrazine, 23 °C, 4 h; (c) 40% KOH; (d) HCl, MeOH; (e) *o*-dichlorobenzene, $CH(OMe)_3$, 120 °C, HCl, MeOH, 24 h.

Finally, treatment with trimethyl orthoformate in methanol (7:1) at 80 °C affords triazolium salt **7a**. The triazolium salt could be precipitated from ethyl acetate and then recrystallized from hot methanol, affording a white crystalline solid. This one-pot protocol can be extended to the synthesis of 4-(trifluoromethyl)phenylhydrazine; however, the cyclization step was performed in triethyl orthoformate in methanol (7:1) at 110 °C in order to obtain clean formation of catalyst **7b**. An X-ray crystal structure of the chloride salt of **7a** is shown in Figure 2.

In efforts to make a des-benzyl analogue of this catalyst by a more economical route, amide activating agents other than trimethyloxonium tetrafluoroborate were investigated. For this purpose, 2-pyrrolidinone **8** was implemented to provide the aliphatic part of the bicyclic skeleton (Scheme 2). A variety of attempts to activate the carbonyl through iminoyl chloride intermediates met with no success. Fortunately, refluxing the amide in acetonitrile with dimethyl sulfate provides the desired amidate, which may be treated with phenylhydrazine in situ. Counterion exchange is achieved by liberating the free hydrazino compound with 40% KOH and treating with methanolic HCl to provide the chloride salt. Cyclization in *o*-dichlorobenzene with trimethyl orthoformate and catalytic HCl provides the achiral catalyst **13**.

In addition to the pyrrolidine framework, the morpholine scaffold appeared attractive since it can be readily prepared from amino alcohols.[13] The synthesis of a chiral bicyclic benzyl-substituted triazolium chloride has been previously reported by Leeper[6] and can typically be extended to other alkyl groups on the morpholine ring. However, this synthetic route can be problematic with some side chains and certain aryl hydrazines.

In our explorations into the asymmetric Stetter reaction, we identified aminoindanol-derived catalyst **18** as

(5) Korotkikh, N. I.; Rayenko, G. F.; Shvaika, O. P.; Pekhtereva, T. M.; Cowley, A. H.; Jones, J. N.; Macdonald, C. L. B. *J. Org. Chem.* **2003**, *68*, 5762−5765.
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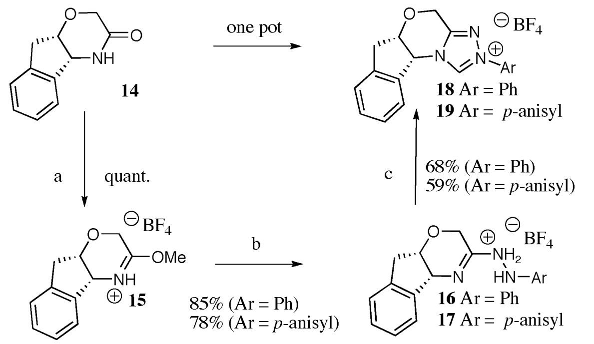
(10) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207−8215.
(11) Smrcina, M.; Majer, P.; Majerová, E.; Guerassina, T. A.; Eissenstat, M. A. *Tetrahedron* **1997**, *53*, 12867−12874.
(12) (a) Pyrrolidinone **6** was initially obtained as a yellow oil that can be used in the subsequent reactions without complications. The yellow solid is obtained after removing the excess solvent in vacuo overnight. (b) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2625−2632. (c) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122−132.
(13) Norman, B. H.; Kroin, J. S. *J. Org. Chem.* **1996**, *61*, 4990−4998.

SCHEME 3. Synthesis of Aminoindanol-Derived Catalyst Precursors[a]



[a] (a) $Me_3O^+BF_4^-$, CH_2Cl_2, 23 °C, 12 h; (b) phenylhydrazine or *p*-anisylhydrazine, 23 °C, 30 min; (c) PhCl, $HC(OEt)_3$, 110 °C, 12 h.

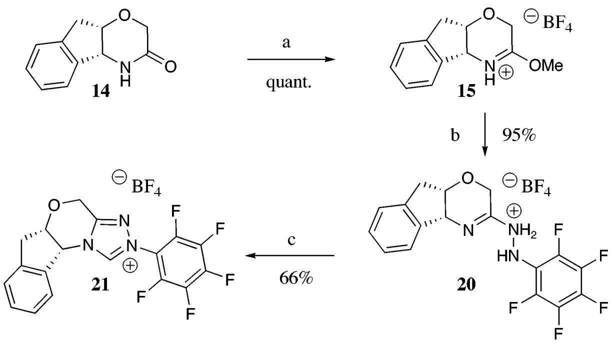
possessing advantageous properties for catalysis. Furthermore, it became evident that the aryl substituent, introduced with various hydrazines, significantly affects the reactivity of these catalysts.[8a,9a] In attempts to address these concerns in the synthesis of these catalysts, we were intrigued by the possibility of the transformation of **14**[14] to **18** in a one-pot procedure (Scheme 3). Formation of amidate **15** from Meerwein's salt in dichloromethane over 12 h at room temperature followed by addition of phenylhydrazine and stirring at room temperature for 30 min gives presumed intermediate **16**. Heating **16** in chlorobenzene with triethyl orthoformate for 12 h provides catalyst precursor **18**. This protocol can be extended to the synthesis of slightly modified salts, as well, as illustrated in the synthesis of *p*-anisyl triazolium salt **19**.

When implementing considerably more electron-deficient aryl hydrazines, we found that the catalyst synthesis had a tendency to be irreproducible during the final cyclization step, often resulting in recovery of unreacted starting material **16** or **17**. As pentafluorophenyl triazolium salt **21** was recently identified as a highly capable catalyst for the intramolecular Stetter reaction,[9a] we needed a reliable method for its production. We have found that minor changes in the cyclization step are essential for a clean formation of this catalyst (Scheme 4).

Standard amidate formation with Meerwein's salt in dichloromethane for 12 h at room temperature and treatment with pentafluorophenyl hydrazine at room temperature for 2 h provides hydrazinium tetrafluoroborate **20**. Evaporation of the solvent followed by addition of triethyl orthoformate and chlorobenzene and heating at 110 °C for 12 h initiates the cyclization. Addition of another 5 equiv of triethyl orthoformate and heating at 110 °C for another 12 h allows for clean triazolium salt formation. Cooling of this mixture to room temperature, with addition of an equivalent volume of toluene (to chlorobenzene), provides triazolium tetrafluoroborate **21** as a light tan solid which is washed with toluene to provide pure material.

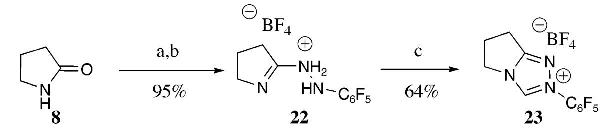
The achiral pentafluorophenyl catalyst can be prepared in a similar manner (Scheme 5). Addition of pentafluorophenyl hydrazine into the amidate derived from Meerwein's reagent and 2-pyrrolidinone **8** in dichloromethane, stirring for 4 h, followed by removal of solvent, provides hydrazinium tetrafluoroborate **22**. Treatment of this compound with 5 equiv of triethyl orthoformate and heating to 110 °C for 12 h yields achiral triazolium salt **23**.

SCHEME 4. Synthesis of Pentafluorophenyl Triazolium Salt 21[a]



[a] (a) $Me_3O^+BF_4^-$, CH_2Cl_2, 23 °C, 12 h; (b) pentafluorophenyl hydrazine, 23 °C, 2 h; (c) PhCl, $CH(OEt)_3$, 110 °C, 24 h.

SCHEME 5. Achiral Pentafluorophenyl Catalyst Precursor 23[a]



[a] (a) $Me_3O^+BF_4^-$, CH_2Cl_2, 23 °C, 12 h; (b) pentafluorophenyl hydrazine, 23 °C, 2 h; (c) $CH(OEt)_3$, 110 °C, 1 h.

In conclusion, we report an improved procedure for the efficient synthesis of a variety of chiral and achiral triazolium salt N-heterocyclic carbene precursors. These are rapidly prepared in modular fashion from common laboratory materials and serve as highly air- and water-stable sources of nucleophilic carbenes. Efforts at expanding the reactivity of these carbenes are currently underway in our laboratories.

Experimental Section

5-Benzyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]-triazol-2-ium tetrafluoroborate (7a): A flame-dried 100 mL round-bottom flask was charged with **6** (1.0 g, 5.71 mmol) and CH_2Cl_2 (40 mL). Trimethyloxonium tetrafluoroborate (0.93 g, 6.29 mmol) was added, and the reaction mixture was stirred overnight at 23 °C. To the pinkish solution was added phenylhydrazine (0.62 mL, 6.29 mmol), and the reaction was stirred overnight. The solvent was removed in vacuo, and the product was used without further purification. Methanol (2 mL) and trimethyl orthoformate (14 mL) were added, and the reaction mixture was stirred at 80 °C overnight. The solvent was removed in vacuo, and the product was precipitated from ethyl acetate to give the desired compound as an off-white/yellow powder. Recrystallization from hot MeOH affords **7a** (1.04 g, 50%) as a white crystalline solid.

2-Pentafluorophenyl-6,10b-dihydro-4*H*,5a*H*-5-oxa-3,10c-diaza-2-azoniacyclopenta[*c*]fluorene tetrafluoroborate (21): A flame-dried 100 mL round-bottom flask was charged with morpholinone **14** (1.000 g, 5.29 mmol) and CH_2Cl_2 (25 mL). Trimethyloxonium tetrafluoroborate (0.783 g, 5.29 mmol) was added and the reaction mixture stirred for 12 h at 23 °C. Pentafluorophenylhydrazine (1.047 g, 5.29 mmol) was then added and allowed to stir for 2 h at 23 °C. The solvent was

(14) Ghosh, A. K.; Mckee, S. P.; Sanders, W. M. *Tetrahedron Lett.* **1991**, *32*, 711−714.

removed in vacuo, and chlorobenzene (50 mL) was added, followed by triethyl orthoformate (2.20 mL, 13.23 mmol). The resulting solution was stirred at 110 °C for 12 h. At this time, additional triethyl orthoformate (2.20 mL, 13.23 mmol) was added, and heating at 110 °C was continued for 12 h. Upon cooling, toluene (50 mL) was added, and the light tan solid product was collected by filtration. This was rinsed with toluene (3 × 5 mL) and heated to 120 °C for 6 h under vacuum to remove residual water to provide triazolium salt **21** (1.56 g, 63%) as a light tan solid.

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Supporting Information Available: Full characterization of compounds **7a**, **7b**, **13**, **18**, **19**, **21**, and **23**, detailed experimental procedures, and X-ray data for **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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