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A Late Stage Strategy for the Functionalization of Triazolium-based NHC catalysts

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Abstract

A strategy for the diversification of triazolium-based catalysts is presented. This method is based on the reduction to the triazoline, which serves as a suitable and stable substrate for Pd-mediated cross-coupling, followed by trityl cation mediated reoxidation to the triazolium.

Keywords

NHC Catalysis; Organocatalysis; asymmetric catalysis

Organocatalysis with *N*-Heterocyclic carbenes (NHC's) has emerged as an important field in synthetic organic chemistry.¹ The ability to impart nucleophilic character to aldehydes is one of the key features of these catalysts. This reversal of polarity, often called *umpolung*,² has led to the discovery of many new reactions.³ While many NHC precatalysts have been reported, triazoliums have gained significant attention.⁴ Our group has contributed to this field with the introduction of new catalysts that have been effective in a variety of reactions (Figure 1).⁵ One important aspect to the success of triazolium based systems is their highly modular synthesis. These catalysts are often formed from the condensation of an amide, hydrazine, and an orthoformate, each of which may be tuned in an effort to achieve improved utility.⁶

Given the importance of structural diversification and substitution on the success of a given catalytic transformation,⁷ access to a wide variety of catalyst structures is crucial. However, syntheses of numerous catalysts can be time-consuming and inefficient. A strategy to overcome this obstacle is late-stage modification of the catalyst. This allows for the rapid formation of a library of new catalysts.⁸ Waser and coworkers accomplished this strategy by revealing a primary amine tethered to a triazolium catalyst (Scheme 1, eqn 1).⁹ This synthetic handle enabled the installation of a thiourea side chain, producing bifunctional catalysts. Bode and coworkers also used a similar amine as a point for manipulation (Scheme 1, eqn 2),¹⁰ and installed a variety of pyrroles providing an array of new catalysts.

Triazoliums based on the *cis*-aminoindanol backbone (such as **2**) have emerged as a dominant scaffold for NHC catalysis. Unfortunately, there remain few reports of modification of this backbone.¹¹ A late-stage manipulation strategy could allow quick access to new analogs of this catalyst. We were inspired by work of Bode and coworkers, who reported the selective bromination of the amide precursor. We envision that a halo-indanol adduct, accessible via a selective bromination,¹² would serve as a suitable substrate in a Suzuki-Miyaura cross-coupling reactions.¹³ A potential issue with this approach is the basic conditions required for this transformation, which can deprotonate the triazolium to form the reactive carbene. Indeed, attempting the cross-coupling on the triazolium gave no desired product, leading only to decomposition of the starting materials.¹⁴

Reduction under mild sodium borohydride conditions easily affords triazolines. These triazolines should be stable to basic conditions, allowing for many kinds of reactions to take place. Concurrent with our own work, Plenio and coworkers recently disclosed the same strategy for the late stage modification of imidazolinium-based catalysts (Scheme 2, eqn 3).¹⁵

With easy access to the bromo-triazoline **4**, we investigated the feasibility of a Suzuki-Miyaura cross-coupling. After finding optimal conditions, we applied this method to elaborate the brominated aminoindanol scaffold (Table 1). Electron-rich arylboronic acids are quite effective as coupling partners. However, more electron-deficient aryl groups result in slightly diminished yields. Sterically hindered systems, such as mesityl or *ortho*-bromo, do not provide any desired products.

After successful derivatization of **4**, we explored conditions to reoxidize to the triazolium salt. For inspiration, we turned to work published by Bildstein and coworkers.¹⁶ While Plenio employed NBS as the oxidant, Bildstein described the oxidation of benzimidazolines with a trityl (triphenylmethyl) salt. While similar, there have been no reports of this transformation with the more electron-deficient triazolines. In the event, this strategy proved effective. Treatment of a triazoline with an equivalent of $\text{Ph}_3\text{C}\cdot\text{BF}_4$ in dichloromethane provides complete conversion to the triazolium salt (Table 2). Precipitation by diethyl ether delivers the compound as a clean powder.

With a method in hand to reoxidize with trityl salts, we explored the potential of this approach to introduce new counterions beyond tetrafluoroborate. This route allows introduction of hexafluorophosphate, hexachloroantimonate, and perchlorate counterions. In terms of substrate, both electron-deficient and electron-rich triazolines can be oxidized by this method. Bulky, chiral triazolines are also tolerated in this reaction. Trityl chloride fails to provide product, most likely due to its covalent C-Cl bond. While isolated yields are presented, these reactions are high yielding when monitored by NMR. The ease of precipitation makes for a useful synthesis.

While this methodology facilitates the rapid access of several diverse triazolium pre-catalysts, we were concerned the increased steric bulk of the catalyst could prove detrimental to reactivity. To test this, we employed these catalysts in an asymmetric

intramolecular Stetter reaction.⁵ These catalysts work in high efficiency while maintaining excellent enantioselectivity.¹⁷

In summary, we present a strategy for the late-stage diversification of triazoliums. Key to this route is a cross-coupling of the triazoline intermediate, which remains stable to basic conditions. Oxidation back to the triazolium salt is easily accomplished by treatment with trityl salts. Substitution of the aminoindanol scaffold does not impede reactivity compared to the native catalyst.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. **Typical Experimental Procedure:** Synthesis of **5a** is as follows: In a glove box, a dry 2-dram glass vial is loaded with $\text{PdCl}_2(\text{PPh}_3)_2$ (7 mg, 0.01 mmol, 0.05 equiv.). The vial is sealed and removed from the glove box. To this vial is added triazoline (100 mg, 0.22 mmol, 1 equiv.), phenylboronic acid (0.32 mmol, 1.5 equiv.) and potassium phosphate tribasic (93 mg, 0.44 mmol, 2 equiv.). Dry THF (1.5 mL) is added followed by water (0.5 mL), as well as a magnetic stir bar. The vial is sealed, secured with Teflon tape, and heated by oil bath at 60 °C for 6 h. Reaction is deemed complete by TLC. The reaction is cooled to rt and 1 mL of brine and 1 mL of EtOAc is added to the reaction. The aqueous fraction is removed, and the organic layer is dried over MgSO_4 . The crude reaction product is filtered and concentrated. The crude product is purified by flash column chromatography, eluting with 0 to 50% EtOAc/Hexanes through basic alumina. 60 mg of dark brown solid was isolated (60% yield). $r_f = 0.5$ (50% EtOAc/Hexane). **$^1\text{H-NMR}$** (300 MHz; acetone- d_6): δ 7.70-7.60 (m, 4H), 7.47-7.35 (m, 4H), 5.68-5.67 (m, 1H), 5.04 (t, $J = 1.1$ Hz, 1H), 4.78 (dd, $J = 5.6, 1.1$ Hz, 1H), 4.64-4.55 (m, 2H), 4.47 (d, $J = 15.6$ Hz, 1H), 3.30-3.28 (m, 2H). **$^{13}\text{C-NMR}$** (101 MHz; acetone- d_6): δ 149.0, 141.6, 140.9, 140.3, 139.6, 129.82, 129.73, 128.49, 128.44, 128.38, 127.8, 127.25, 127.18, 127.16, 126.8, 125.6, 123.8, 123.2, 77.1, 73.6, 62.3, 59.2, 34.8. **MS** calcd for $\text{C}_{24}\text{H}_{16}\text{F}_5\text{N}_3\text{O}$: 457.4, found 458.1 (M+H). **IR**: (neat) 2914, 1626, 1504, 1479, 1429, 1340, 1307, 1055, 1039, 977 cm^{-1} . $[\alpha]_D^{23} = -39.17$ ($c = 2.4$, acetone).

Figure 1.
Representative Triazolium Pre-catalysts

Scheme 1.
Previous Strategies for Late-Stage Manipulation

Scheme 2.
Triazolines as substrates for cross-coupling

Table 1

Suzuki-Miyaura Cross-coupling

Reaction conditions: Triazoline **4** (1 equiv.), Boronic acid (1.5 equiv.), Potassium Phosphate (2 equiv.) Pd(PPh₃)₂Cl₂ (5 mol %), THF/H₂O (3:1), heated to 60 °C

Table 2

Oxidation of Elaborated Triazolines

Table 3

Oxidation with Trityl Salts

Intramolecular Stetter

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