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N-Heterocyclic Carbene Triazolium Salts Containing Brominated Aromatic Motifs: Features and Synthetic Protocol

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We dedicate this work to the late Supreme Court Justice Ruth Bader Ginsburg.

Abstract: In this work, we provide a brief overview of the role of *N*-aryl substituents on triazolium *N*-heterocyclic carbene (NHC) catalysis. This synopsis provides context for the disclosed synthetic protocol for new chiral *N*-heterocyclic carbene (NHC) triazolium salts with brominated aromatic motifs. Incorporating brominated aryl rings into NHC structures is challenging, probably due to the substantial steric and electronic influence these substituents exert throughout the synthetic protocol. However, these exact characteristics make it an interesting *N*-aryl substituent, because the electronic and steric diversity it offers could find broad use in organometallic- and organo-catalysis. Following the synthetic reaction by NMR guided the extensive modification of a known protocol to enable the preparation of these challenging NHC pre-catalysts.

Keywords: Arylhydrazine · De-silylation · NHC · Organocatalysis · Triazolium salts

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Low-energy barriers between competing reaction pathways are the double-edged sword at the core of organocatalysis. On the one hand, these small energy differences make it challenging to control organocatalytic selectivity and reproducibility, on the other, it is possible to control selectivity and reactivity by slight modifications to the catalyst structures. *N*-heterocyclic carbenes (NHC) have been widely applied in numerous classes of organocatalytic reactions due to their highly tunable structures and triazolium-based NHCs have been particularly instrumental in enantio- and chemo-selective reactions. Notably, the substitution pattern on their aromatic motif shows a striking difference in catalytic and

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chemical activities under different reaction setups. This catalytic versatility is well demonstrated by two well-studied examples of *N*-aryl NHC substituents, pentafluoro-phenyl and mesityl, which are often compared due to their diverse electronic and steric characteristics (Fig. 1).

A study by Bode and coworkers[1] meticulously assessed their diverging effects on catalytic reactions of α-functionalized aldehydes and provided mechanistic insight on the nature of this difference. They suggest that this difference stems from the reversible formation of the *N*-pentafluoro-phenyl acyl anion adduct compared to the irreversible formation of this adduct using the *N*-mesityl-substituted catalyst (Fig. 1E).

Their conclusions are based on experimental differences in deprotonation, namely, mesityl undergoes partial deprotonation in the presence of DBU while pentafluoro-phenyl is fully deprotonated. This result is supported by a series of esterification experiments in which the catalytic activity was evaluated for different NHC catalysts (select examples are presented in Fig. 1).

Following up on these intriguing observations, Smith, O'Donoghue and coworkers[2] examined the role of different *N*-aryl substituents by monitoring protonated NHC–aldehyde acyl anion adducts *in situ* by NMR (Fig. 2). They studied reaction rates as well as the protonated acyl anions' equilibrium constants, acidities, and deuterium exchange rates. They asserted based on the equilibrium observed for the protonated acyl anion adducts that, at least in the system they studied, the addition of the aldehyde to the NHC was reversible, even using *N*-mesityl triazolylidene. Interestingly, they introduced an *N*-2,4,6-trichloro-phenyl substituent, which presumably has electronic properties similar to those of *N*-pentafluoro-phenyl and steric hindrance similar to *N*-mesityl. The reaction rates revealed that the 2,4,6-trichloro-phenyl-substituted NHC performed very similarly to the pentafluoro-phenyl-substituted one, while the deuterium exchange rate of the trichloro-phenyl was in mid-range between the pentafluoro- and mesityl-substituted one. However, the equilibrium constants revealed the trichloro-phenyl substituted NHC as be-

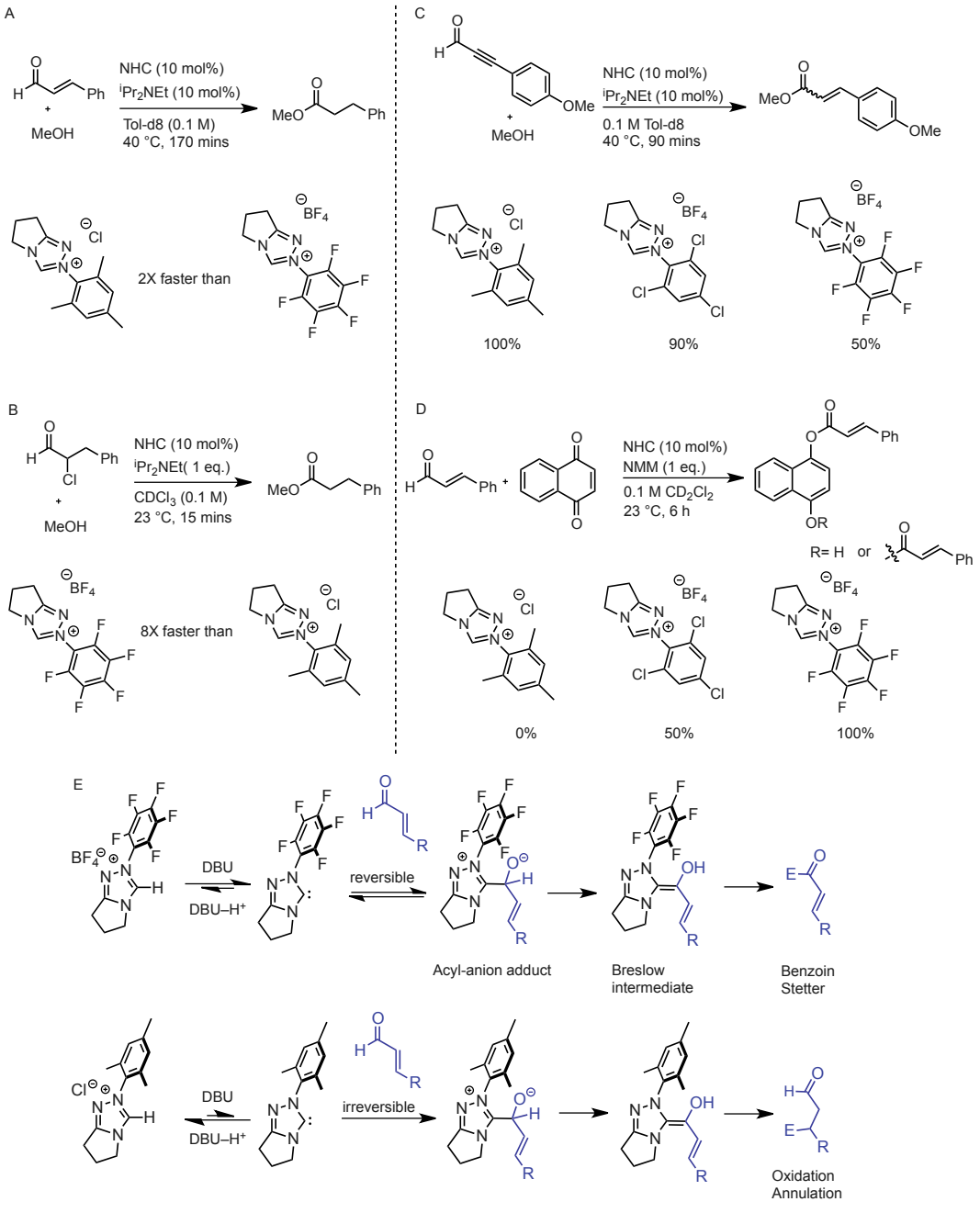


Fig. 1. Examples presented by Bode and coworkers[1] of different reactions with *N*-pentafluoro and *N*-mesityl NHCs: (A) redox esterification of cinnamaldehydes and (B) α-chloroaldehyde, (C) intramolecular Stetter reaction, (D) hetero Diels-Alder reaction. (E) Proposed mechanistic rationalization for the differences in reactivity and selectivity between *N*-pentafluoro and *N*-mesityl NHCs.

ing more stable than the pentafluoro but at the same magnitude, while the mesityl was less stable (with *K* values of 601, 521 and 143 (M^{-1}) respectively). The authors speculate that increased stability is due to a better accommodation of the acyl anion adduct, which stems from the propensity of large 2,6-substituents to enforce the *N*-aryl ring to adopt an orientation orthogonal to the triazole ring.

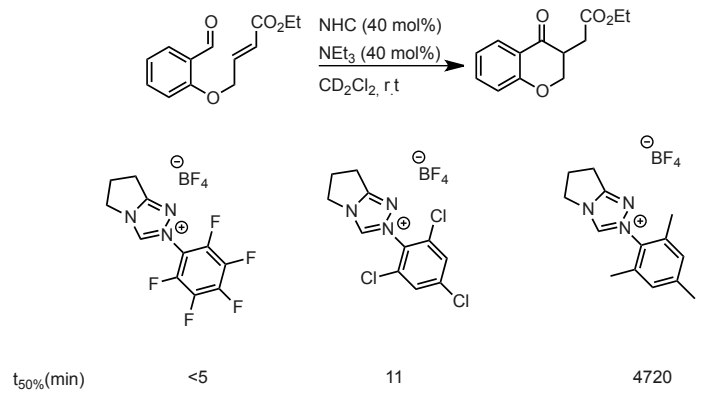


Fig. 2. Smith, O'Donoghue and coworkers[2] examination of different aryl substituents. $t_{50\%}$ represents the time it took to reach 50% conversion.

Lee, Rovis and coworkers[3] studied the influence of *N*-aryl substituents on both computationally and experimentally derived acidities of protonated NHC precursors. The computed acidities are well correlated with the experimental results, however, since the experiments were based on mass spectrometry gas-phase proton transfer reactions between the NHC precursors and various bases, the resolution in values was limited to the pK_a values of the bases (Fig. 3). Thus, the authors selected to correlate the computed pK_a values with the diastereoselectivity of a model reaction (see Fig 4 below), which demonstrated that the triazolium salt acidities are key in predicting the selectivity of the resulting catalyst.

In a study by Connon and coworkers[4] the influence of the *N*-aryl substituent was examined on the cross-coupling benzoin condensation of benzaldehyde and *o*-bromobenzaldehyde (Fig. 4). This report presents a similar selectivity for *N*-pentafluoro-phenyl- and *N*-2,4,6-trichloro-phenyl-substituted NHCs, while the

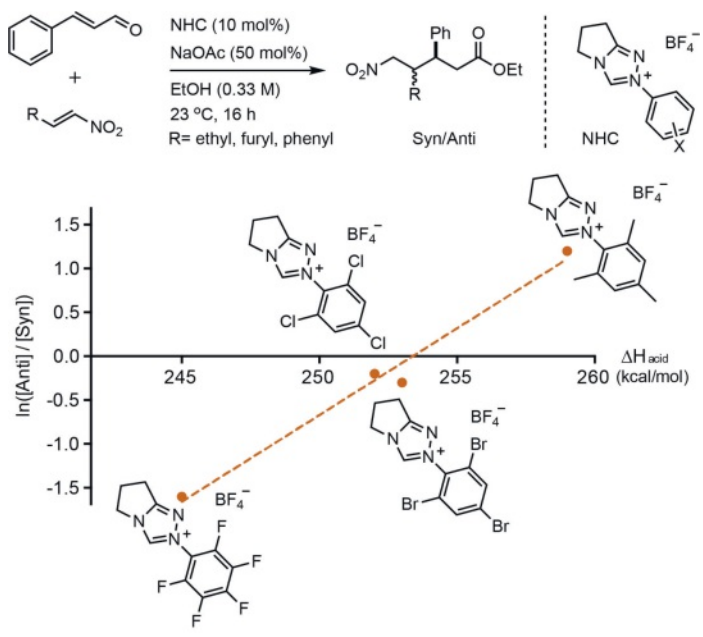
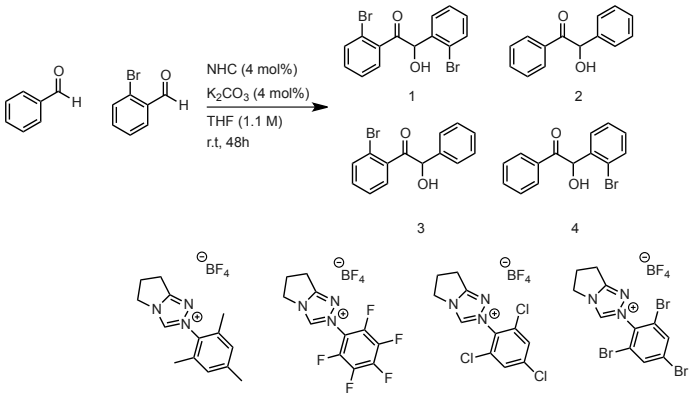


Fig. 3. Acidity-selectivity relationship for NHC-catalyzed homoenolate addition of enals to nitroalkenes by Lee, Rovis and coworkers.[3]

N-2,4,6-trichloro-phenyl substituent diverges in selectivity. This result points to non-trivial underlying electronic and steric effects that cannot always be foreseen by a single parameter such as the NHC pre-catalyst pK_a. If that were the case, 2,4,6-trichloro and the 2,4,6-tribromo would be expected to have similar activities in the mid-range between *N*-pentafluoro-phenyl and N-mesityl substituted NHCs.



Product	Yield %	Yield %	Yield %	Yield %
1	0	4	1	1
2	1	21	18	1
3	0	11	7	0
4	1	66	75	15

Fig. 4. Comparison of NHC pre-catalysts in the cross-benzoin reaction by Connon and coworkers.[4]

We employed DFT optimizations of the structures of the *N*-mesityl, *N*-pentafluoro-phenyl and *N*-2,4,6-tribromo-phenyl triazolium salts in order to compare their steric and electronic properties (Fig. 5). This optimization gave rise to a few unsurprising characteristics that provide clear reasoning for the mid-range acidity of the 2,4,6-tribromo *N*-aryl substituent. Sterimol parameters[5] serve as a steric description of the *N*-aryl substituent with L being the length of the substituted ring, B_1 is the minimal width perpendicular to the principal axis L and B_5 is the maximal width perpendicular to the principal axis L (Table 1). NPA charges of the acidic carbon (C_2) and the substituted nitrogen (N_{11}) serve as a description of electron distribution, such that the more negative value corresponds to a higher electron occupancy and vice versa. Dipole moments and their Cartesian components are computed upon NPA charges and taken with respect to a shared coordinate system. The torsion angle is taken between the triazolium ring and the *N*-aryl substituent. The results support the hypothesis that the 2,4,6-tribromo-phenyl holds a similar steric nature to that of the mesityl substituent, based on the Sterimol values and the torsion angle. The charges indicate that *N*-2,4,6-tribromo-phenyl more closely resembles *N*-pentafluoro-phenyl in terms of its electronic properties. However, the dipole moments, combine steric and electronic characteristics, thus are less conclusive, putting 2,4,6-tribromo-phenyl somewhere between the two extremes. With these considerations in mind we set out to synthesize several chiral *N*-tribromo-phenyl substituted NHC pre-catalysts.

Many NHC triazolium salts with a variety of aromatic motifs have previously been prepared,[6] however, the introduction of brominated aryl rings remains challenging, probably due to the substantial steric and electronic influence these substituents exerted throughout the synthetic protocol.[7,8] The common synthetic route for the preparation of NHC triazolium catalysts includes the following steps. The reaction begins with a nucleophilic at-

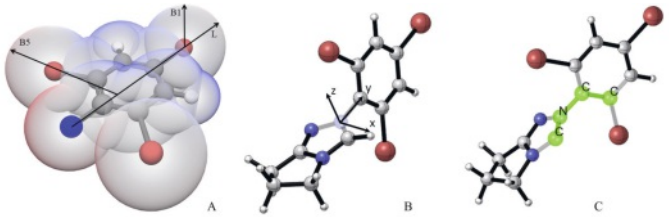
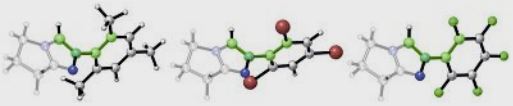


Fig. 5. Computed physical parameters exemplified upon *N*-2,4,6-tribromo NHC. (A) Sterimol steric parameters. (B) Shared coordinate system with origin at N_{11}. (C) Highlighted atoms for which the torsion angle was calculated.

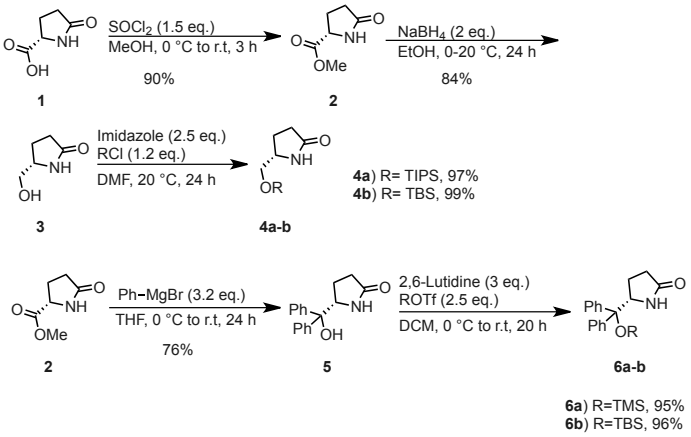
Table 1. Computed physical parameters

			
	Mesityl	**2,4,6-tribromo**	**pentafluoro**
B_1 [Å]	2.81	2.88	2.32
B_5 [Å]	4.37	4.79	3.70
L [Å]	6.15	6.98	5.83
Torsion	72.48°	91.77°	53.42°
y axis dipole [eÅ]	–0.921	–1.06	–1.78
Total dipole [eÅ]	1.14	1.27	1.90
C2 NPA [e][a]	0.267	0.287	0.284
N11 NPA [e][a]	–0.119	–0.131	–0.128

[a]e represents the elementary charge unit

tack of 2-pyrrolidinone by trimethyloxonium tetrafluoroborate (Me_3OBF_4) to form an iminium salt, which then reacts with a hydrazine to form a hydrazone. The latter step introduces the aromatic motif into the resultant NHC catalyst and the hydrazine then undergoes cyclization to afford an NHC pre-catalyst (Scheme 1). To obtain the chiral version of these catalysts where the 2-pyrrolidinone contains a silyl protected hydroxyl group, the cyclization is followed by a de-protection step (step 4).

In our search for an appropriate procedure that will enable the incorporation of brominated aromatic motifs, we first applied our previously optimized protocol for the preparation of NHC triazolium catalysts.[9] Our aim was to provide a synthetic protocol for two types of chiral catalysts with different steric profiles, thus, we prepared a precursor with a benzylic pendant hydroxyl group (**3**) and another with two phenyl rings at the benzylic position (**5**). In the presence of thionyl chloride, the commercially available starting material (*S*)-pyroglutamic acid (**1**) is converted into an ester (**2**). The reduction of ester **2** with sodium borohydride forms primary alcohol **3**, whereas the reaction of **2** with the Grignard reactant, phenyl magnesium bromide, leads to tertiary alcohol **5**. Selectively protecting the hydroxyl on **3** and **5** with silyl chloride and silyl triflate lead to the formation of the corresponding silyl ethers **4** and **6** (Scheme 2).



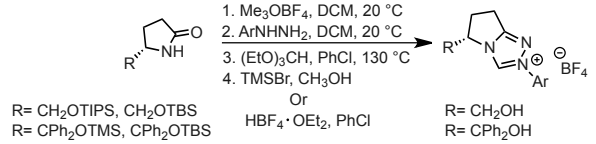
Scheme 2. Synthesis of functionalized pyrrolidinones **4a**,**b** and **6a**,**b**.

To prepare a brominated NHC triazolium salt we were required to first synthesize 2,4,6-tribromophenyl hydrazine from 2,4,6-tribromoaniline. We optimized a known procedure and achieved a 50% boost in reaction yield (Scheme 3).[4]

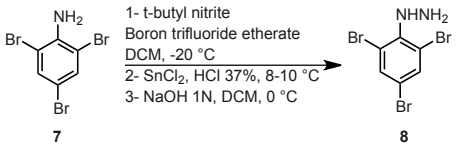
Using compounds **4a**,**b**, and **6a**,**b** and 2-pyrrolidinone (**4c**) as starting materials and hydrazine **8** as the brominated phenyl source, we applied our previously optimized procedure for the preparation of the NHC pre-catalyst.[4] Unfortunately, this effort resulted in only one of the corresponding products in low yield (Scheme 4A).

With the goal of identifying the key to improving these results, we closely examined the reaction that provided catalyst **9a** by following its progress in ^{1}H NMR. By analyzing the conversion over time, we realized that the timing of each step was crucial and longer reaction times led to the formation of byproducts that interfered with the following steps while shorter reaction times did not lead to full conversion and hampered the isolation of products. Once we identified the optimal timing for each reaction step, the reaction yields for **9a** substantially improved. We then applied the new found timing to the rest of the tested starting materials, but once again did not manage to identify general conditions for the full set of catalysts. The only additional product we were able to prepare was **9b** in 24% yield. Nonetheless, we were able to de-protect the TIPS group on **9b**, affording another hydroxyl pre-catalyst (**9f**, Scheme 4B).

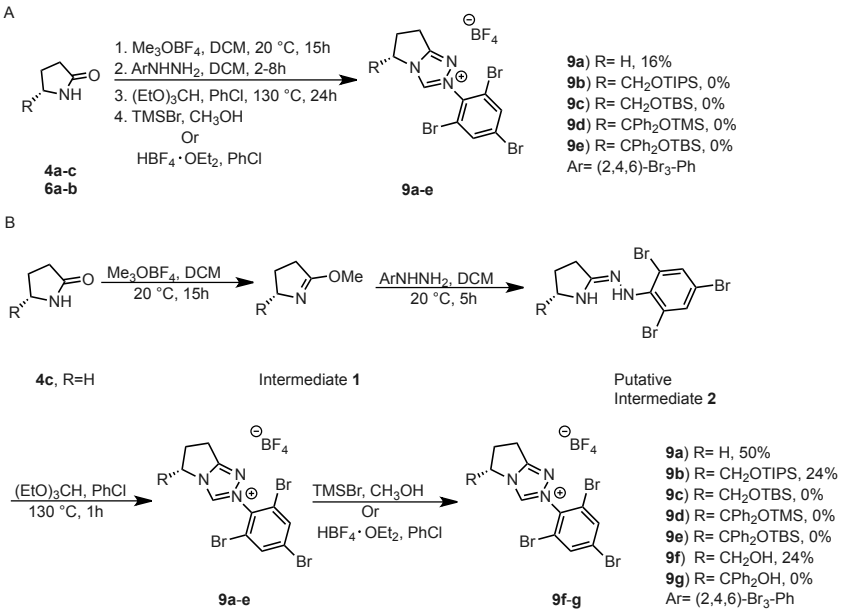
Following the reaction progress by NMR provided important insights regarding the phenyl hydrazine addition. We managed to isolate intermediate **1** and thus could follow its disappearance and the formation of an additional intermediate, which we were unable to isolate. Based on the crude NMR and the proposed mechanism, we assume this intermediate has the structure of putative intermediate **2** (Scheme 4B). We speculated that the reaction was impeded by the stability of putative intermediate **2**. To face this issue, we decided to focus again on optimizing the reaction conditions of



Scheme 1. General procedure for the synthesis of NHC triazolium catalysts.



Scheme 3. Optimized conditions for the synthesis of 2,4,6-tribromophenyl hydrazine.

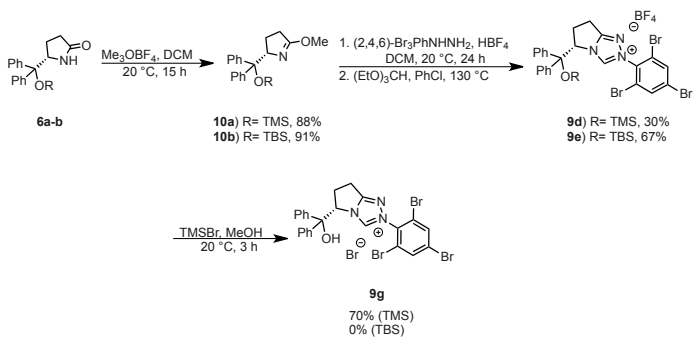


Scheme 4. (A) One pot synthesis of NHC triazolium salts **9a–e**. (B) Optimized timing of reaction steps achieved by following reaction progress in ^{1}H NMR.

9a (Table 1 in the Supplementary Information). We found that both Lewis and Brønsted acids stabilized the reaction intermediates, but Lewis acids stabilized intermediate **1** to the extent that it was unreactive. Based on the proposed mechanism of the first step, the release of the tetra-fluoroboric acid (HBF_4) is essential to the process, as it can protonate intermediate **1** making it a better electrophile in the reaction with the phenyl hydrazine. However, the addition of HBF_4 to the reaction mixture also stabilized intermediate **1**, which brought the reaction to a halt.

To further investigate the role of HBF_4 in reaction, we isolated intermediate **1**, which allowed the application of different amounts of HBF_4. The desired isolated intermediate was stable enough to be purified by column chromatography, the isolated intermediate for material **4c** evaporated with the solvent, but starting materials **6a**,**b** resulted in isolated intermediates (**10a**,**b**) in high yields. Reacting the resulting imine ethers **10a**,**b** with the brominated phenyl hydrazine **8** in the presence of precisely one equivalent HBF_4 led to the conversion to putative intermediates **2**, which in turn was successfully cyclized and afforded a substantial amount of the desired protected NHC precursors (**9d**,**e**). The application of more than one equivalent of HBF_4 over-stabilizes intermediates **1**, preventing the reaction from moving forward and using less yielded a new, unknown intermediate that failed to cyclize properly. Eventually, by a de-protection we were able to produce pre-catalysts **9f** in a good yield (Scheme 5).

In conclusion, we have presented a rational analysis and optimization of triazolium NHC synthesis steps in an effort to incorporate a tri-brominated phenyl substituent. We report the synthesis of five new NHC pre-catalysts in practical yields (**9b**, **9d**, **9e**, **9f**, and **9g**) and the improvement of the yield of a known pre-catalyst (**9a**). These new catalysts could find broad use in organometallic- and organo-catalysis due to the diversity they offer in their electronic and steric attributes compared to known NHC catalysts.



Scheme 5. Chiral NHC triazolium salt two-pot synthesis reaction under optimized conditions.

Supplementary Information

Supplementary information is available on *https://www.ingentaconnect.com/content/scs/chimia*

Acknowledgments

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