Synthetic Methods

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Tuning the Reactivity of Isocyano Group: Synthesis of Imidazoles and Imidazoliums from Propargylamines and Isonitriles in the Presence of Multiple Catalysts**

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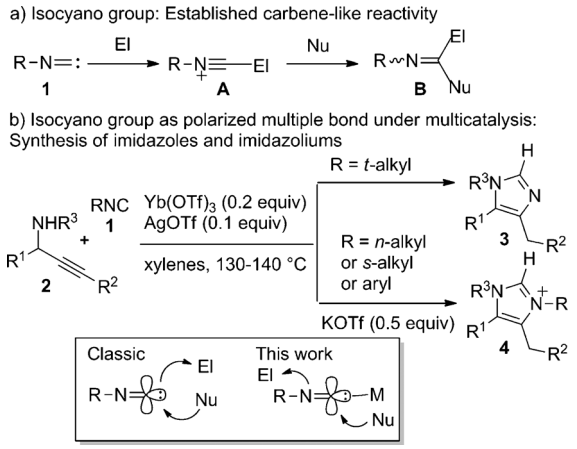
Abstract: *The reaction of propargyl amines with tert-butylisonitrile in the presence of a catalytic amount of both $Yb(OTf)_3$ and AgOTf afforded imidazoles, whereas the same reaction with primary and secondary alkylisonitriles, as well as arylisonitriles, in the presence of three metal salts [$Yb(OTf)_3$/AgOTf/KOTf] resulted in the 1,3,4,5-tetrasubstituted imidazoliums in excellent yields. Both chiral amines and chiral isonitriles can be used to provide corresponding chiral heterocycles without racemization. In this multiple catalytic system, $Yb(OTf)_3$ catalyzed the insertion of isonitriles to the N–H bond of amines, AgOTf catalyzed the 5-exo-dig cyclization of the resulting amidine nitrogen to the tethered triple bond, and KOTf promoted the salt metathesis, thus providing at the same time the counterion to the imidazolium. Against common knowledge, the isocyano group acted in these reactions as a polarized triple bond instead of conventional carbene-like function.*

The development of catalytic domino processes has attracted much attention among synthetic chemists.[1] One of the recent and promising advances in this field is the emergence of dual catalysis for the construction of complex molecular architectures from simple starting materials. Different combinations including metal/organo,[2] metal/enzyme,[3] organo/organo,[4] and metal/metal catalysts[5] have been exploited for this purpose. In developing such processes, one generally pays particular attention on the sequence design and the compatibility of the multicatalytic systems to facilitate the planned multiple catalytic cycles. In spite of the recent intensive research efforts, the types of reactions incorporated in multicatalytic processes are still limited and examples aimed at developing new reactivity patterns of given functional groups remain scarce.

We have been interested in isonitrile chemistry for years[6] and have recently initiated a research program aimed at exploiting the new reactivity profiles of isocyano groups.[7] It is well-established that the divalent carbon atom of the isonitriles (**1**), known to have a pronounced nucleophilicity, reacts readily with electrophiles to afford the nitrilium intermediate **A**, which upon addition of a nucleophile provides the α-adduct **B** (Scheme 1a). Indeed, most of the



Scheme 1. Reactivity patterns of isonitriles. Tf = trifluoromethanesulfonyl.

isonitrile-based organic transformations, including the powerful Passerini three-component reaction[8] and the Ugi four-component reaction,[9] were developed by relying on the carbene-like reactivity of the isocyano group.[10] We report herein multicatalytic reactions in which the isocyano group acts formally as a polarized triple bond rather than a carbene (Scheme 1b).[11] Thus, reaction of propargylamines with *tert*-butylisonitrile in the presence of a catalytic amount of $Yb(OTf)_3$ and AgOTf afforded the 1,4,5-trisubstituted imidazoles **3**, whereas the same reaction with the primary and secondary alkylisonitriles, as well as arylisonitriles in the presence of $Yb(OTf)_3$/AgOTf/KOTf afforded the 1,3,4,5-tetrasubstituted imidazoliums **4** in excellent yields. In this multiple catalytic system, $Yb(OTf)_3$ catalyzed the insertion of the isonitrile to the N–H bond of amine, AgOTf catalyzed the 5-*exo*-dig cyclization of the resulting amidine to the tethered triple bond, and KOTf promoted the salt metathesis thereby providing at the same time the counterion to the imidazolium. Imidazoles and imidazolium salts, are important heterocycles

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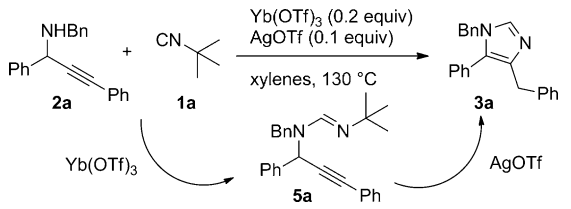
in pharmaceuticals and in organic synthesis, and have attracted chemists for many years.[12] However, efficient and general catalytic methods are still under intensive development.[13–15]

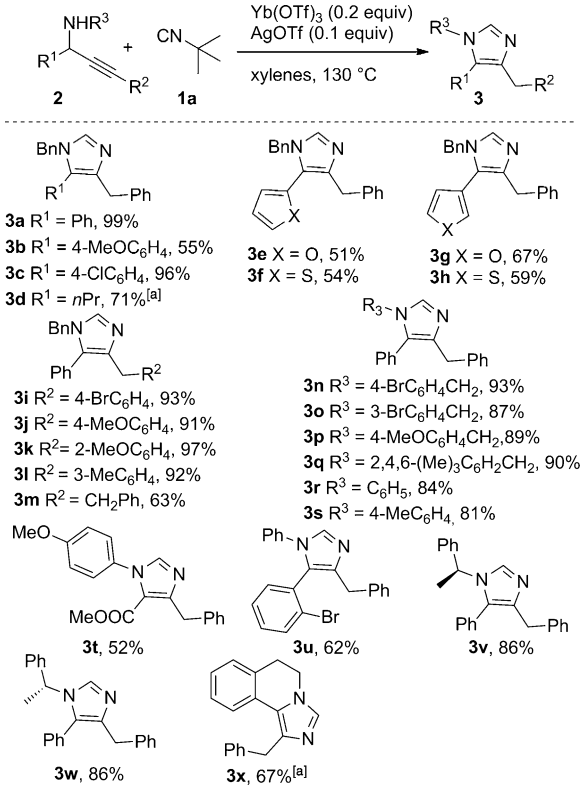
The reaction between *tert*-butylisonitrile (**1a**) and *N*-benzyl-1,3-diphenylprop-2-yl-1-amine (**2a**)[16] was initially investigated by varying the metal salts, the solvents, and the temperature (Scheme 2). Key observations are summarized



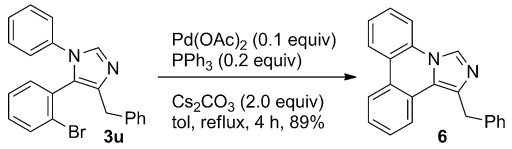
Scheme 2. Multicatalysis: Synthesis of 1,4,5-trisubstituted imidazoles.

as follows: a) $Y(OTf)_3$, $La(OTf)_3$, and $Yb(OTf)_3$ were effective Lewis acids to catalyze the insertion of isocyanide to the N–H bond of the secondary amine, with $Yb(OTf)_3$ being the best, to afford the amidine **5a** in a quantitative yield. Interestingly, other metal salts such as CuCl, AgOAc, AgOTf, $NaAuCl_3$, which are known to catalyze/promote the amine insertion to isonitriles,[17] failed to produce **5a**, probably because of the preferential coordination of these π-acidic metal salts to the triple bond, thus inhibiting the insertion reaction; b) $Yb(OTf)_3$ is an ineffective catalyst for the conversion of amidine **5a** into **3a**. Silver salts, especially AgOTf, catalyzed the 5-*exo*-dig cyclization of **5a** leading to **3a** in a quantitative yield;[18] c) $Yb(OTf)_3$ and AgOTf are compatible and the two catalytic cycles did not interfere with each other. Therefore in practice, there was neither need to isolate the amidine intermediate nor to introduce the two catalysts sequentially;[19] d) Xylenes gave the best result among solvents screened (THF, 1,4-dioxane, DMF, DCE, toluene and xylene). Overall, the all-in-one protocol consisted of heating a xylenes solution (130 °C) of **1a** and **2a** in the presence of $Yb(OTf)_3$ (0.2 equiv) and AgOTf (0.1 equiv). Under these reaction conditions, the imidazole **3a**, whose structure was confirmed by X-ray structural analysis, was isolated in 99 % yield.[20]

The scope of this imidazole synthesis turned out to be very general (Scheme 3). Aryl groups with different electronic properties including heterocycles (**3e**–**h**) and alkyl groups can be introduced into the 1-, 4-, and 5-positions of imidazoles. The reaction was not sensitive to steric hindrance as compound **3q** (R^3 = 2,4,6-trimethylbenzyl) can be obtained in 90 % yield. Chiral propargylamines can be converted into enantioenriched imidazoles without racemization as is evidenced by the synthesis of the two enantiomers **3v** and **3w**. The 1-benzyl-5,6-dihydroimidazo[5,1-*a*]isoquinoline **3x**, an important bicyclic compound in medicinal chemistry,[21] is readily synthesized from the corresponding cyclic secondary amine. It is interesting to note that when N-aryl propargylamines (R^3 = Ar, **3r**–**u**) were used as substrates, the competitive direct cyclization of **3r**–**u** leading to quinolines was not observed.[22]



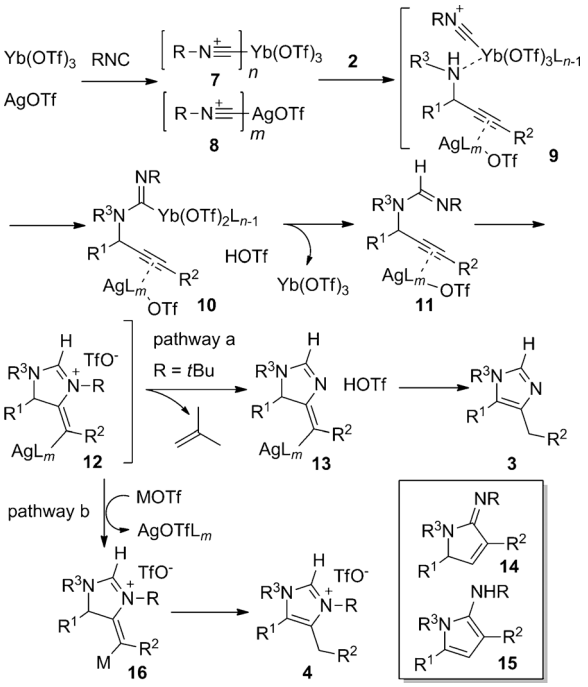
Scheme 3. Scope of reaction. [a] Reaction was performed at 140 °C.



Scheme 4. Further structural elaboration of functionalized imidazole.

The so-obtained imidazole could be further elaborated to more complex polycyclic structure (Scheme 4). For example, heating a toluene solution of **3u** in the presence of a catalytic amount of $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 afforded 1-benzylimidazo[1,5-*f*]phenanthridine (**6**) in 88 % yield.[20,23]

It is known that isonitrile can form a complex with both Yb^{III}[24] and Ag^{I}[25] salts. In addition, we found that the pre-synthesized complex $Ag(OTf)(t\text{BuNC})_n$ has the same catalytic activity as AgOTf.[26] It is therefore reasonable to assume that both $Yb(OTf)_3$ and AgOTf, upon mixing with isocyanide, will form the complexes **7** and **8**, respectively (Scheme 5). Ytterbium triflate, which is azophilic, would further coordinate to the amine,[27] while silver triflate, which is more π-acidic,[28] would prefer to coordinate to the triple bond to produce **9**. Migrative insertion from **9** would produce **10** and TfOH. Salt metathesis between **10** and TfOH would produce the amidine **11** with the concurrent regeneration of $Yb(OTf)_3$. Intramolecular nucleophilic addition of the amidine nitrogen atom to the silver-coordinated triple bond through a 5-*exo*-dig mode afforded the intermediate **12**, which upon dealkylation (R = *t*Bu), would produce **13** and TfOH.[29] Protonation of **13** followed by double-bond isomerization would produce **3** with

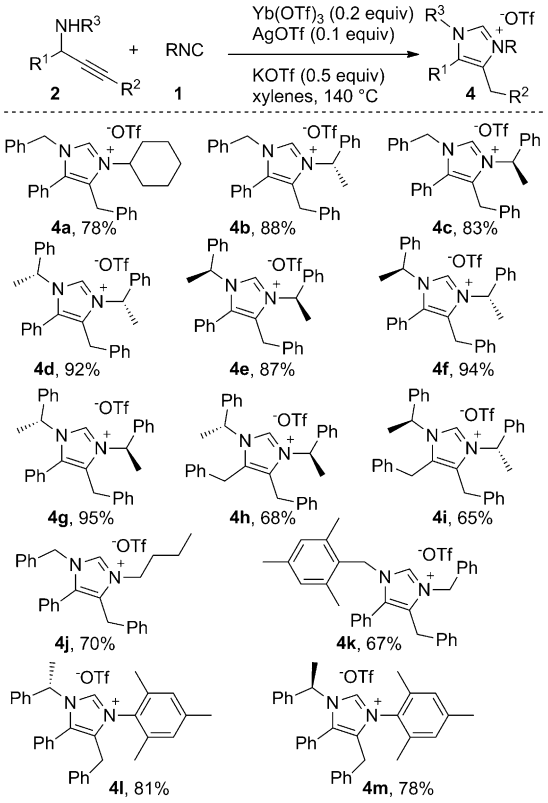


Scheme 5. Reaction pathways leading to imidazoles and imidazolium salts.

the concurrent regeneration of AgOTf. We stress that alternative cyclization of **10** to **14**[30] and its isomerization product **15**, resulting from the normal carbene-like reactivity of isonitrile, was not isolated, probably because of the rapid metathesis of the C–Yb bond.[30]

Based on the above mechanistic hypothesis, we assumed that it would be possible to divert the reaction towards the formation of imidazolium if the dealkylation step (pathway a; Scheme 5) was slowed down and if additional metal salt (MOTf) was added to promote the salt metathesis with **12** (pathway b; Scheme 5). This path would produce **16** with concurrent regeneration of AgOTf. The former, upon protonation and double-bond isomerization would then afford the imidazolium **4**.

Experimentally, it was found that simply heating a xylenes solution (140 °C) of **1** and **2** in the presence of three metal salts, $Yb(OTf)_3$ (0.2 equiv), AgOTf (0.1 equiv), and KOTf (0.5 equiv), afforded the salts **4** in excellent yields. As summarized in Scheme 6, the reaction is applicable to a wide range of substrates including primary and secondary alkylisonitriles, as well as arylisonitriles. Chirality can be introduced to the products through both **1** and **2** without erosion of enantiopurity and a variety of chiral imidazoliums including the C_2-symmetric ones (**4h**, **4i**) were readily accessible.[31] Bulky isonitriles such as 2,4,6-trimethylphenylisonitrile was tolerated to afford the chiral **4l** and **4m** in excellent yields. It is interesting to note that chiral imidazolium salts of type **4** have been seldom used as chiral ionic liquids or as chiral N-heterocyclic carbene precursors in asymmetric synthesis, probably because of their low synthetic accessibility.[32] We expect that the present general and robust synthesis could facilitate the exploitation of this subclass of imidazolium salts.



Scheme 6. Scope of imidazolium synthesis.

In summary, we developed novel and efficient syntheses of imidazoles and imidazoliums in which the isocyano group acted formally as a polarized triple bond rather than a carbene function. Reaction of propargylamines with *tert*-butylisonitrile in the presence of a catalytic amount of $Yb(OTf)_3$ and AgOTf afforded 1,4,5-trisubstituted imidazoles, while reaction of propargylamines with primary and secondary alkylisonitriles, as well as arylisonitriles, in the presence of $Yb(OTf)_3$/AgOTf/KOTf provided 1,3,4,5-tetrasubstituted imidazoliums in excellent yields. In the latter reaction, three task-specific metal salts, belonging to f-, d-, and s-blocks, acted synergistically to drive the reaction towards the formation of chiral tetrasubstituted imidazolium salts, which are difficult to access by existing synthetic methodologies.

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