α-Lithio quinuclidine *N*-oxide (Li-QNO): A new base for synthetic chemistry†

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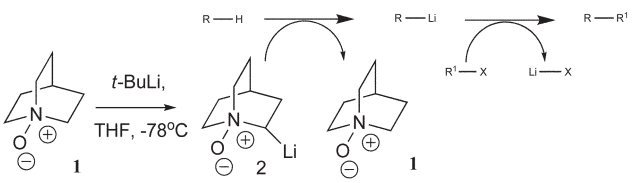
α-Lithio quinuclidine *N*-oxide (Li-QNO) behaves as a strong non-nucleophilic base and an HMPA mimetic in a tandem process, in a range of synthetically useful reactions

Numerous reactions in organic synthesis require the additive hexamethylphosphoric triamide (HMPA) to render them viable.[1] HMPA is a dipolar aprotic solvent that is able to form strong ligand–cation complexes. As a result of this it enhances the rates of a wide variety of main group organometallic reactions. It also has an influence on regio- and stereochemistry of key reactions such as enolate formation. HMPA can also enhance the formation and reactivity of carbanions, ylide reactivity and carbanion regioselectivity (1,2 *versus* 1,4 addition). HMPA is thought to act as a metal binding agent that disrupts the aggregation states that enolates normally exist in.[2] HMPA is a listed mutagen and as such its use is limited in both industry and academia. Several other substances including 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) have been employed as replacements for HMPA but all have limitations.[3] We have previously reported the successful use of quinuclidine *N*-oxide (QNO) **1** as a replacement for HMPA in several key reactions including the benzylation of the dianion of methyl 3-nitropropionate, the nitroaldol reaction between nitropropane and benzaldehyde, the Michael addition of 1,3-dithiane to cyclohexenone and the $SiCl_4$ mediated cleavage of cyclohexene oxide.[4] Most importantly QNO is non-mutagenic.[4]

In this communication we wish to report the use of α-lithiated QNO (Li-QNO) **2** as a new base, which combines high basicity with low nucleophilicity. In a tandem process, QNO **1** is lithiated with *tert*-butyllithium to generate Li-QNO **2**. The Li-QNO **2** then acts as a powerful base and deprotonates a substrate molecule added to the system. This generates an equivalent of QNO **1**, which then acts as an HMPA mimetic, enhancing the reactivity of the carbanion that has been formed (Scheme 1). The reagent system is flexible so that an excess of QNO **1** can be treated with 1 equivalent of *tert*-butyllithium to generate 1 equivalent of Li-QNO with the remaining QNO **1** present as an additive, to enhance the reactivity of the carbanion. In the cases we have studied this reagent system is as effective or superior to the use of alkyllithiums or LDA in conjunction with the mutagenic HMPA as an additive.

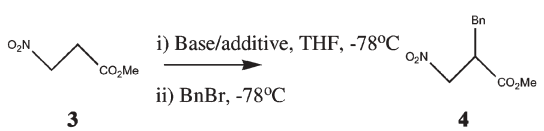


Scheme 1

Central to the success of this reagent is a reliable method for the synthesis of anhydrous QNO. We have found that this is conveniently carried out by the reaction of ozone with quinuclidine in either diethyl ether or hexane at −78 °C.[6–8] The QNO precipitates out of solution and the solvent can be removed under vacuum. The reaction solvent, usually THF can then be added. Anhydrous QNO is only sparingly soluble in THF at room temperature. We have also found that ultrasonic agitation of QNO in THF for 10 min prior to the addition of *tert*-butyllithium facilitates the formation of the Li-QNO anion. Presumably the sonication aids the dispersion of the QNO, and after sonication we can dissolve *ca.* 0.3 g of QNO in 30 ml of THF at room temperature. We have examined the use of Li-QNO as a base in a number of synthetically useful transformations.

Initially, we studied the benzylation of the dianion of methyl nitropropionate **3**.[5] Treatment of methylnitropropionate **3** with 2 equivalents of Li-QNO followed by addition of benzyl bromide gave the product **4** in 34% yield. Significantly, no addition of the quinuclidine *N*-oxide anion into the ester was observed. This was comparable to when LDA was used as the base in the presence of 2 equivalents of HMPA. We took this as evidence that Li-QNO removes the two acidic protons in the substrate **3** regenerating 2 equivalents of QNO, which serves to promote the alkylation step. Furthermore, when an additional 3 equivalents of QNO were present as an additive, benzylation occurred in almost quantitative yield, superior to the case when 5 equivalents of HMPA were used (Scheme 2).

We then turned our attention to the Wittig olefination of 3-phenylpropyltriphenylphosphonium bromide **5** with



Base (2eqs)	Additive (equivs)	Yield **4** (%)
LDA	0	8
LDA	HMPA (5.2)	85
LDA	DMPU (10)	85
LDA	QNO (5.0)	78
Li-QNO	QNO (3.0)	99

Scheme 2

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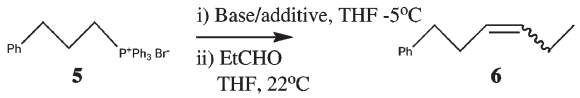


Base	Additive	Yield (%)	(*Z*)-**6**/(*E*)-**6**
BuLi	0	46	83/17
BuLi	HMPA (35%)	44	92/8
BuLi	DMPU (35%)	39	93/7
Li-QNO	0	54	92/8
Li-QNO	QNO (4 equivs)	65	>95/5

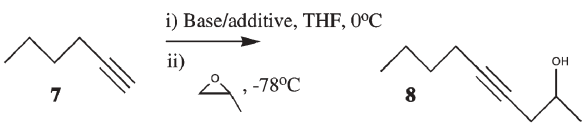
Scheme 3

propionaldehyde. It has been demonstrated that the (*Z*)-content of the alkene product **6** can be significantly increased by the use of either HMPA or DMPU.[3,9] The presence of either additive as a cosolvent in 35% volume in THF affords a greater than 9 : 1 mixture of the product alkene in favor of the (*Z*)-stereoisomer. Again we chose Li-QNO (1 equivalent) to carry out the deprotonation of the phosphonium salt in place of *n*-butyllithium/HMPA. This gave the desired product in 54% as a 92 : 8 mixture of *E* : *Z* isomers When an additional 4 equivalents of QNO were present as an additive, not only was the (*Z*)-alkene favoured in a ratio of greater than 20 : 1 but also the overall yield of **6** was improved to 65% (Scheme 3).

The ring opening of propylene oxide with lithium 1-hex-1-ynide prepared from hex-1-yne **7** to give the alcohol **8** is a very inefficient reaction in the absence of any additive.[10] It can be improved by the addition of either 17% HMPA or to a slightly lesser degree with 50% DMPU[3] (both as cosolvents). 1 Equivalent of Li-QNO proved to be a competent base to deprotonate alkyne **7** and in the presence of 4 equivalents of QNO as an additive, the yield of the reaction was 55% (Scheme 4).

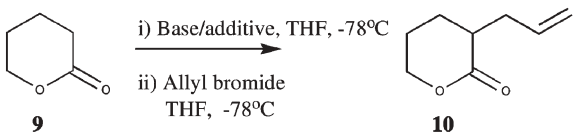
The alkylation of lactones is an important synthetic transformation which frequently requires the presence of HMPA to proceed efficiently. Treatment of δ-valerolactone **9** with 1 equivalent of LDA followed by addition of allyl bromide gives poor yields of the alkylated compound **10**. By adding 0.2[12] to 1.2[13] equivalents of HMPA the yield of the product is increased to 41–73%. Use of 1 equivalent of Li-QNO followed by addition of allyl bromide gave the product in an excellent 89% yield. Again, no addition of the Li-QNO into the carbonyl group was observed (Scheme 5).

The final reaction we chose to investigate was the addition of 2-lithiodithiane derived from 1,3-dithiane **11** to an α,β-unsaturated carbonyl system. It is known that an additive such as HMPA or DMPU can be used to switch the regioselectivity of such reactions from 1,2- to 1,4-addition.[3,11] We have also previously



Base	Additive	Yield **8** (%)
BuLi	0	5
BuLi	HMPA (17%)	70
BuLi	DMPU (50%)	59
Li-QNO	0	11
Li-QNO	QNO (4 equivs)	55

Scheme 4



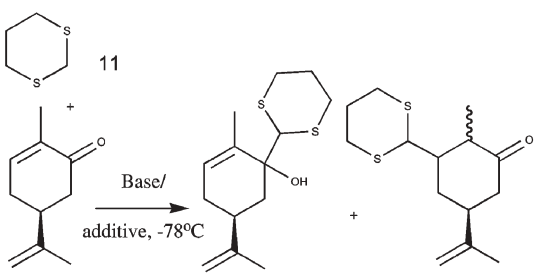
Base	Additive	Yield **10** (%)
LDA	HMPA (1 equiv)	41
Li-QNO	0	89

Scheme 5

demonstrated the efficacy of QNO in this role with cyclohexenone[4] as the α,β-unsaturated ketone. Using the conditions described in this paper dithiane can be deprotonated with 1 equivalent of Li-QNO in the presence of 4 equivalents of QNO as an additive. Addition of cyclohexenone at −78 °C gives the 1,4 addition product in 90% with >95 : 5 selectivity. (*S*)-(+)-Carvone (**12**) was then employed as the α,β-unsaturated ketone. When no QNO was present (*tert*-BuLi as the base) the 1,2-addition product **13** was formed exclusively in 78% yield. By using 1 equivalent of Li-QNO as the base we were able to obtain a mixture of the **13** and **14** in a ratio of 3 : 1 in favour of the 1,2-addition product **13** in an overall yield of 65%. In the presence of 5 equivalents of QNO the 1,4-addition product **14** was favoured[14] in a ratio greater than 20 : 1 and in 93% yield overall (Scheme 6).

Finally, the quinuclidine *N*-oxide **1** can be recycled at the end of the reaction. After quenching the reaction with water, and addition of an appropriate organic solvent, the QNO partitions into the aqueous layer and the desired product into the organic layer. Since QNO is highly hygroscopic we have found it convenient to remove the water, dissolve the residue in methanol and reduce the QNO back to quinuclidine using catalytic hydrogenation, in quantitative yield. The resulting quinuclidine can be purified using standard techniques and can be readily reused.

In conclusion, we have shown that Li-QNO **2** can effectively replace both an organolithium base and an additive such as HMPA or DMPU in several key reactions known to require the presence of an additive. In many cases the additive effects of QNO are superior to that of HMPA. We are currently exploring other anionic reactions known to require cation complexing additives. We are also involved in the synthesis of further functionalised QNO derivatives, which include the presence of stereogenic



Base	Additive	1,2-(**13**)/1,4-(**14**)	Yield (%)
tert-BuLi	0	>20/1	78
Li-QNO	0	75/25	65
Li-QNO	QNO (4 equivs)	<1/20	93

Scheme 6

centres, and additional metal binding sites in an effort to enhance reactivity, selectivity and solubility.

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