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Base-Catalyzed Asymmetric α-Functionalization of 2-(Cyanomethyl)azaarene *N*-Oxides Leading to Quaternary Stereocenters

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Supporting Information

ABSTRACT: A simple, new strategy for the direct asymmetric α-functionalization of 2-alkyl azaarenes is described. Specifically, a Brønsted base catalyzed conjugate addition of substituted 2-cyanomethylpyridine (and pyrazine) *N*-oxides to acrylate equivalents to afford hitherto elusive 2-*tert*-alkyl azaaryl adducts with high enantioselectivity (up to 94% *ee*) is realized. Extension of the method to the α-amination reaction by using azodicarboxylate esters as electrophiles is also demonstrated. Key for success is the *N*-oxide functionality of substrates that acts as a removable activating and stereodirecting group. A bifunctional Brønsted base catalyst bearing a squaramide with an attached bulky silyl group is also disclosed.

Ortho-substituted pyridines, and more generally azaarenes, are widespread structural motifs,[1] with the congeners that are chiral by virtue of an α-stereogenic *o*-substituent constituting a relevant subset. Several catalytic approaches have recently been reported for the enantioselective synthesis of such chiral units via α-deprotonation of the corresponding 2-alkylazaarene (Figure 1a).[2] With simple 2-alkylazaarenes (R: H, alkyl, etc.), substrate activation requires a (super)stoichiometric strong base (LiHMDS),[3] thus compromising practicality. Milder conditions have been developed for the α-functionalization of preactivated substrates, i.e. those with electron-withdrawing substituents (EWG) in either the azaarene ring (*p*-nitroazaarenes, polyheteroarenes) or the Cα (α-ester, amide, electron-deficient aryl) or both (strategy 2).[4,5] In these cases, α-stereogenic 2-substituted azaarenes can be produced with high enantioselectivities by means of a chiral Pd(II),[4a] Ni(II),[4b] or amine[5] catalyst and no base, or only a catalytic weak base, being added. However, none of these methods address the generation of a quaternary α-stereocenter,[6] an issue of general importance in organic synthesis,[7] and of particular significance to the present context given the interest in 1,1-diaryl quaternary compounds as potential pharmacophores.[8] Here we describe an enantioselective α-functionalization of *o*-substituted azaarenes that is complementary to the known procedures in several aspects: (i) successfully affords hitherto elusive all-carbon quaternary stereocenters, (ii) relies on a Brønsted base activation strategy using newly designed chiral bifunctional organocatalysts, and (iii) uses azaarene *N*-oxides, more specifically substituted 2-cyanomethyl azaarene *N*-oxides,[9] as enabling substrates (Figure 1b).

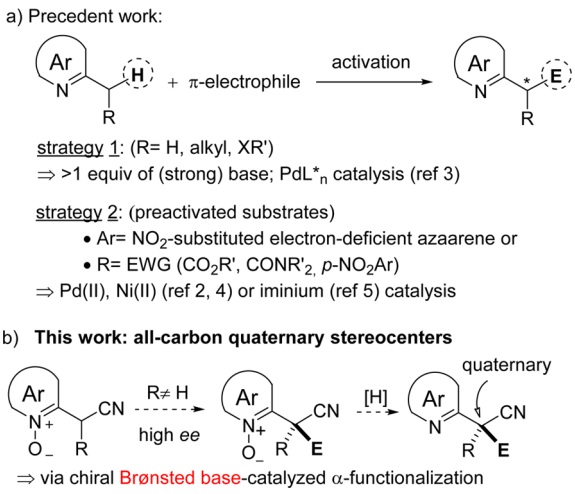

Figure 1. Enantioselective routes to *o*-substituted azaarenes.

Two key elements that make 2-cyanomethyl azaarene *N*-oxides perfect substrate candidates *a priori* are their relatively high CH Brønsted acidity as compared to most alkylazaarenes[10] and the presence of the N → O group as a potentially coordinating site for catalyst binding.[11] Considering this, one might expect that bifunctional chiral Brønsted bases[12] would suffice for an effective α-deprotonation and subsequent stereoselective bond formation. As far as we know azaarene *N*-oxides have not been investigated within the context of asymmetric C(sp^3)−H functionalizations.[13,14]

At the outset, we studied the behavior of 2-cyanoalkylpyridine **1** under Brønsted base catalysis conditions and selected as a reaction partner enone **2**, an acrylate surrogate well suited for organocatalytic conjugate additions.[15] As data in Scheme 1 show, the reactions in the presence of typical cinchona-based bifunctional Brønsted base catalysts **C1**−**C3**[16] were sluggish, with low conversion after an extended reaction time (96 h) at room temperature and poor enantioselectivity. The reactivity increased substantially when the corresponding *N*-oxide[17] **4a** was employed instead (Scheme 2). Thus, conversions of ∼70% were reached after 2 days at ambient temperature, almost complete at 40 °C, but with yet suboptimal enantioselectivity (75% *ee* with **C3**). After some additional screening,[18] we tested the new

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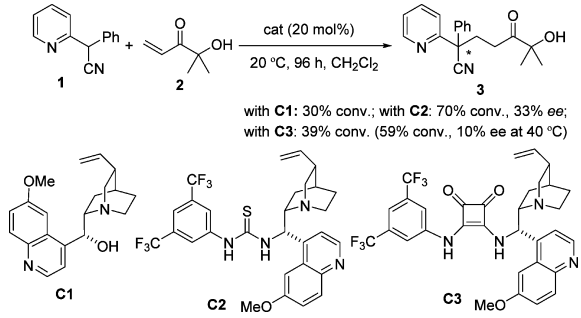
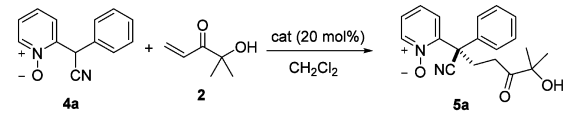
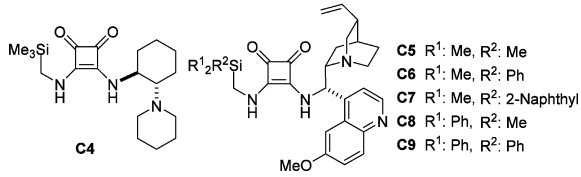
Scheme 1. Difficulties in the Brønsted Base Catalyzed Reaction of 2-Cyanomethylpyridine 1



Scheme 2. Catalyst Screening for the Reaction of 2-Cyanomethylpyridine *N*-Oxide 4a and Enone 2



cat.	conditions	conv. (%)	*ee* (%)	cat.	conditions	conv. (%)	*ee* (%)
C1	20 °C, 48 h	72	22	**C5**	40 °C, 20 h	100	90
C2	20 °C, 40 h	60	17	**C6**	20 °C, 64 h	100	92
C3	40 °C, 48 h	92	75	**C7**	40 °C, 24 h	100	84
C3	20 °C, 48 h	72	88	**C8**	40 °C, 24 h	100	85
C4	40 °C, 96 h	83	58	**C9**	20 °C, 64 h	100	81

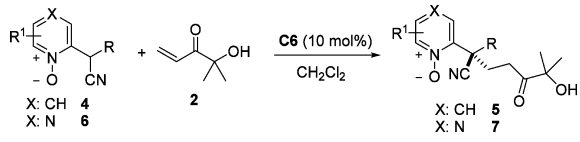


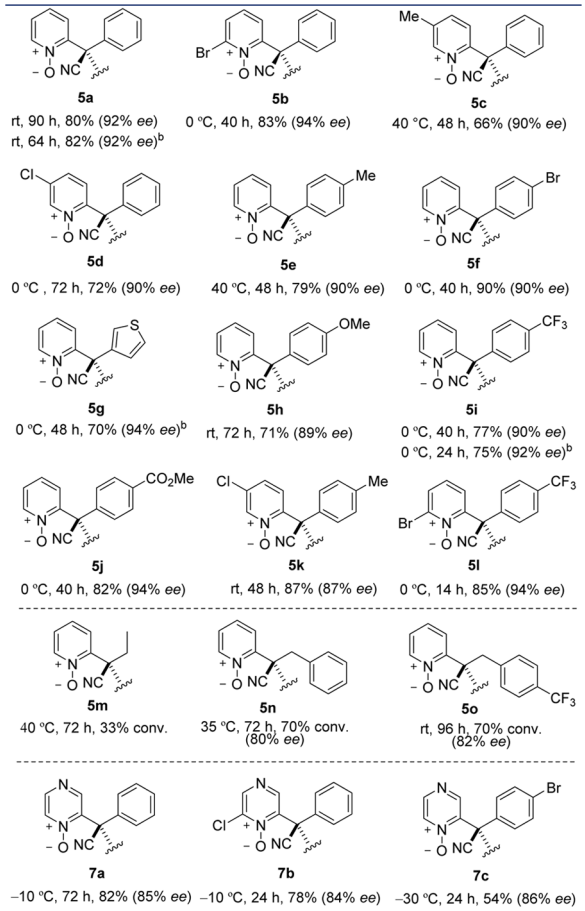
squaramide catalysts[19] **C4**–**C9**, which show as a novel feature a R_4Si site that might play a steric function or even participate in some specific *N*–*O* → *Si* interaction.[20] Gratifyingly, we observed that while catalyst **C4** performed poorly, the reaction between **4a** and **2** catalyzed by **C5** and **C6** led to the highest selectivity (90% and 92% *ee*, respectively) in dichloromethane at temperatures in the range 20–40 °C.

Catalyst **C6** was thus selected to explore the scope of the reaction with a range of 2-cyanomethyl azaarene *N*-oxides (Table 1). It was found that under these conditions the reaction tolerated well pyridine *N*-oxides **4** with both electron-releasing and -withdrawing groups attached at different positions of the pyridine ring. Similarly, substrates bearing both electron-rich and -poor aryl substituents at C*α* were equally effective in providing the corresponding addition adducts **5** in generally very good yield and high enantioselectivity. Nonetheless, the method was less tolerant with the corresponding *α*-alkyl substituted 2-(cyanomethyl)azaarene *N*-oxides **4** (R = alkyl, products **5m**–**o**). Then it was proven that variation of the azaarene system did not apparently affect the reaction course, as the corresponding 2-cyanomethylpyrazines **6** added efficiently to **2** to afford the quaternary 1,1′-diaryls **7a**–**c** in good yields. In these latter cases somewhat lower enantioselectivity was obtained, although they were still acceptable considering the challenge posed by these types of targets.[9]

It was subsequently proven that these 2-cyanomethylpyridine *N*-oxides may also work as enabling substrates for stereoselective *α*-heterofunctionalization reactions under conditions similar to those mentioned above. For example, the pyridine *N*-oxide **4a** reacted with di(*tert*-butyl) azodicarboxylate **8** in the presence of

Table 1. Scope of the Reaction of *α*-Substituted 2-(Cyanomethyl)azaarene *N*-Oxides with 2 Catalyzed by C6[a]





[a]Reactions conducted on a 0.2 mmol scale in 1 mL of CH_2Cl_2 (molar ratio of **4** or **6**/**2**/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase. [b]20 mol % **C6** was used.

10 mol % **C8** to afford *α*-aminated adduct **10a** in 90% isolated yield and 81% *ee*. The same reaction using catalyst **C9** led to product with 90% *ee*. The scope of this *α*-amination process using either di(*tert*-butyl) or dibenzyl azodicarboxylate **8** or **9** as the amination reagent was briefly investigated for a range of 2-cyanoalkylpyridine *N*-oxides. As data collected in Table 2 show, reactions proceeded successfully to give products **10** and **11** in good yields and *ee*'s, with catalyst **C9** providing the best results for most of the entries. Once again, the parent pyridine **1** proved to be less efficient for these transformations. For instance, the reaction of **1** and di(*tert*-butyl) azodicarboxylate **8** in the presence of 10 mol % catalyst **C8** proceeded to a limited extent of 30% conversion after 15 h at 0 °C.

The detailed mechanism of these catalytic transformations as well as the precise role played by each element involved remains unclear. However, data in Figure 2 indicate that the *N*-oxide group and its *ortho*-relationship to the cyanoalkyl substituent are key for optimal reaction outcome.[21] As a general trend, for the three positional isomers *ortho*, *meta*, and *para*, the corresponding pyridine *N*-oxide was more reactive than the parent pyridine in

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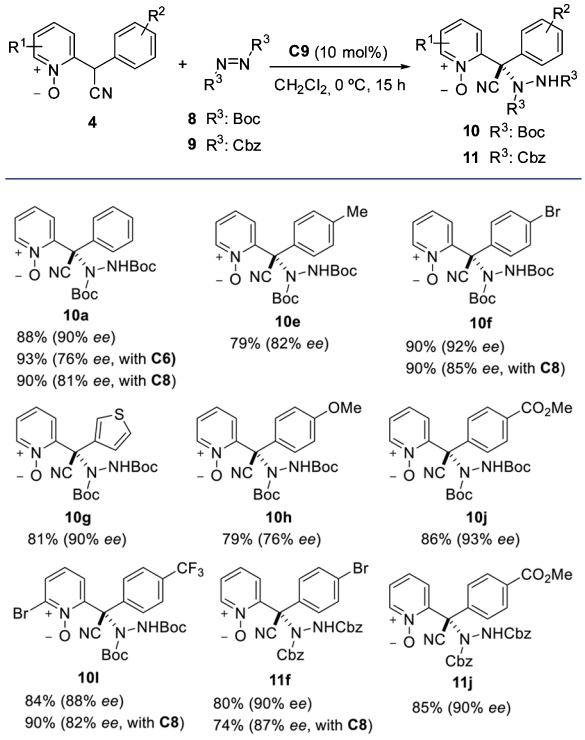
Table 2. α-Amination Reaction of 4[a]



[a]Reactions conducted on a 0.2 mmol scale in 1 mL of CH_2Cl_2 at 0 °C (molar ratio of **4**/**8** or **9**/catalyst 1:1.5:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase.

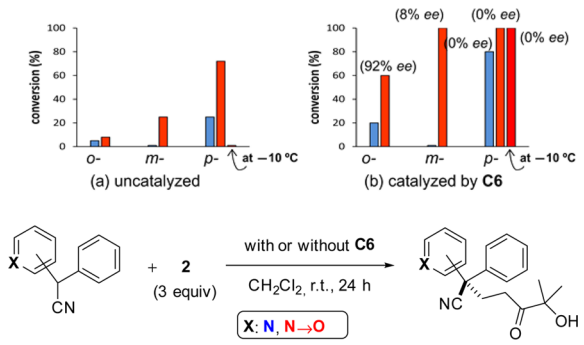
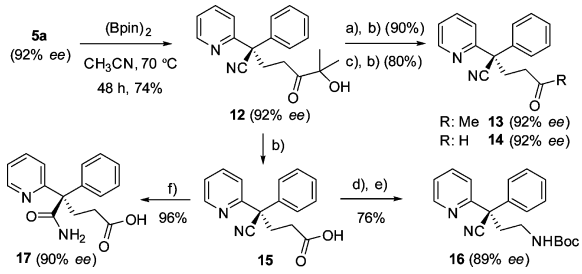


Figure 2. Conversion after 24 h for the reactions of **2** with *o*-, *m*-, and *p*-substituted cyanoalkylpyridines and pyridine *N*-oxides.

both the catalyzed and uncatalyzed reactions. In fact, among the six experiments involving cyanoalkylpyridines, only that using *p*-cyanoalkylpyridine in the presence of **C6** provided practical conversion after 24 h, leading to a racemic product. Equally important is the position of the *N*-oxide group relative to the cyanoalkyl substituent on the ring. Among the three cyanoalkylpyridine *N*-oxides, the *meta* and *para* isomers proved to be inherently more reactive than the *ortho* isomer, also in the presence of catalyst **C6**, although both led to essentially a racemic product. In contrast, the *ortho* isomer led to 92% *ee*.

Adducts obtained from these catalytic transformations can be modified in several ways. For instance, reduction of the *N*-oxide group on adduct **5a** by treatment with $(Bpin)_2$[22] afforded pyridine **12** in 74% isolated yield and unaltered enantioselectivity (92% *ee*, Scheme 3). Furthermore, elaboration of the ketol moiety in adducts by applying well established protocols allows

Scheme 3. Elaboration of 5a into Quaternary 1,1′-Diaryls[a]



[a]Reagents and conditions: (a) MeMgBr, 0 °C, 6 h; (b) $NaIO_4$, $MeOH/H_2O$, rt, 1 h; (c) BH_3·THF, THF, 0 °C, 2 h, then MeOH; (d) Et_3N, DPPA, toluene, 80 °C, 2 h; (e) ^tBuOH, 50 °C, 16 h; (f) H_2SO_4 (conc.), rt, overnight.

the corresponding ketone (**13**), aldehyde (**14**), or carboxylic acid (**15**) product to be furnished from a common single intermediate and with formation of acetone as the only organic waste. These results are of particular interest in that the direct conjugate addition of azaarene *N*-oxide **4** to simple enones, i.e. methyl vinyl ketone, or unsaturated esters, i.e. methyl acrylate, did not work under the present catalytic conditions. In addition, the reaction of **4** with acrolein afforded the corresponding 1,4-addition adduct, but with a poor 15% *ee*. Another illustration of the synthetic versatility of adducts is shown by transformation of the nitrile carboxylic acid **15** into the protected amine **16** and amide **17**, respectively. On the other hand, the configuration of adducts **5a** and **10a** was established by single crystal X-ray analysis,[23] and for the remaining adducts it was assigned by assuming a uniform reaction mechanism.

In summary, a mild and highly enantioselective carbo- and hetero-α-functionalization of 2-cyanomethylazaarene *N*-oxides is developed as the first direct and asymmetric entry to α-quaternary alkylazaarenes. The *N*-oxide group plays a strategic role as a removable activating and stereodirecting element in conjunction with newly designed bifunctional squaramide-Brønsted base catalysts bearing a bulky silyl group. While the specific role played by the silyl group during catalysis is not clear yet,[24] its easy variation makes this new subclass of squaramides very attractive for further asymmetric transformations under proton transfer conditions. Work to address these issues is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13385.

Crystallographic data for **5a** (CIF)
Crystallographic data for a **10a** derivative (CIF)
Experimental details, NMR spectra, HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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(21) Unlike the *meta* and *para* isomers, the ^{1}H NMR spectrum of the *ortho* isomer shows significant changes when recorded in the absence or the presence of 1 mol equiv of **C6**, respectively. For details, see the SI.

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(23) CCDC-1437384 (compound **5a**) and CCDC-1453241 (*p*-nitrobenzoyl amide of **10a**) contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. See the SI for details.

(24) In a preliminary prospect, these Brønsted bases proved to be efficient catalysts in reactions involving *C*-nucleophiles other than azaarene *N*-oxides. For example, the reaction of *tert*-butyl phenylcyanoacetate with **2** promoted by **C6** led to the corresponding Michael addition product with 94% *ee*. See the SI for details.

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