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The Lewis basicity of amines on the Legault iodonium Lewis acidity scale†

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Diaryliodonium–amine complexes are proposed as key intermediates in metal-free C–N coupling reactions. Herein, ^{1}H NMR titration is used to quantify association constants (K_a) between diaryliodonium triflates and synthetically relevant amines from which the amine Lewis basicity (LB_I) parameter is calculated. Compared to anionic Lewis bases, distinct solvent effects are observed.

Aryl amines are prevalent scaffolds in approved drugs and agrochemicals.[1] Among the numerous ways to synthesize these motifs, the metal-free arylation of amines with diaryliodonium salts is a convenient method because it merges the simplicity of nucleophilic aromatic substitution (S_NAr) with the improved scope of a reductive ligand coupling pathway (Scheme 1a).[2–8] The mechanism that has been proposed for these reactions involves the coordination of the amine lone-pair with the iodonium(III) center prior to deprotonation of the amine and reductive ligand coupling (Scheme 1b).[4,6] Although logical, there is relatively little support for this type of interaction with primary and secondary amines and anilines that have been the subject of prior synthetic studies. Ochiai and co-workers have quantified the coordination of pyridine and related derivatives (*e.g.* bipy and terpy) with diphenyliodonium tetrafluoroborate in DCM,[9] and Legault and co-workers have quantified the coordination of quinuclidine and 4-pyrrolidylpyridine with several diaryliodonium salts (Scheme 1c).[10] Additionally, as part of a synthetic study on the arylation of DABCO, Karchava and co-workers have isolated an X-ray structure suggesting an interaction between DABCO and diphenyliodonium triflate,[5] but the strength of this interaction is not known. These pioneering examples have provided evidence for amine–iodonium binding events, but they have been conducted in different solvents and therefore are difficult to compare; and the prior studies represent a small subset of amines with limited relevance to synthetic studies.

Legault and Mayr recently developed an iodonium Lewis acidity scale which is an ideal way to benchmark non-covalent interactions of iodine(III) centers with Lewis basic groups.[10] In this Communication we measured the association constants (K_a) between three representative diaryliodonium salts, for which the Lewis acidity (LA_I) has been established,[10] and 6 amines that have been used in arylation reactions with diaryliodonium salts, including tertiary, secondary, and primary amines, as well as an aromatic amine (Scheme 1d).[4–6] Moreover, we calculate the Lewis basicity (LB_I) of the amines and discuss the distinct solvent effects observed for interactions of diaryliodonium salts with anionic and neutral Lewis bases.

We initiated these studies by selecting three diaryliodonium triflates as reference Lewis acids (**1–3**; Fig. 1a).[10] We also considered the structurally related tertiary amine, quinuclidine **4**, not as a reference Lewis base, but rather as a point of comparison with the amines studied in this work because the Lewis basicity (LB_I = 2.25) and sensitivity (s_I = 0.85) of **4** is known (Fig. 1).[10] Although, K_a values for association of heterocyclic amines, such as pyridine, with diaryliodonium salts are known,[9,10] we shifted our focus to classes of amines that have precedent in C–N coupling reactions[4–7] so that the Lewis basicity (LB_I) of these amines could be determined and used as a parameter in future synthetic and mechanistic studies (**5–10**; Fig. 1b). As part of this study, we also determined the LA_I for two additional unsymmetrical diaryliodonium salts, **11** and **12**, which are novel arylation reagents (Fig. 1c).

The ^{1}H NMR titration of the diaryliodonium host with increasing equivalents of the amine guest was used to measure the equilibrium constant (K_a) between the reference diaryliodonium salts **1–3** and amines **5–10** in MeCN-d_3 at room temperature (Fig. 2 and ESI†). We obtained K_a values that ranged from 30–728 M^{-1} for aliphatic and aromatic amines **5–10**. A plot of $\log K_a$ *vs.* LA_I revealed linear correlation from which the s_I and LB_I values were determined for amines **5–10** according to the equation developed by Legault (eqn (1) and Fig. 2).[10]

$$\log K_a = s_I LA_I + LB_I \quad (1)$$

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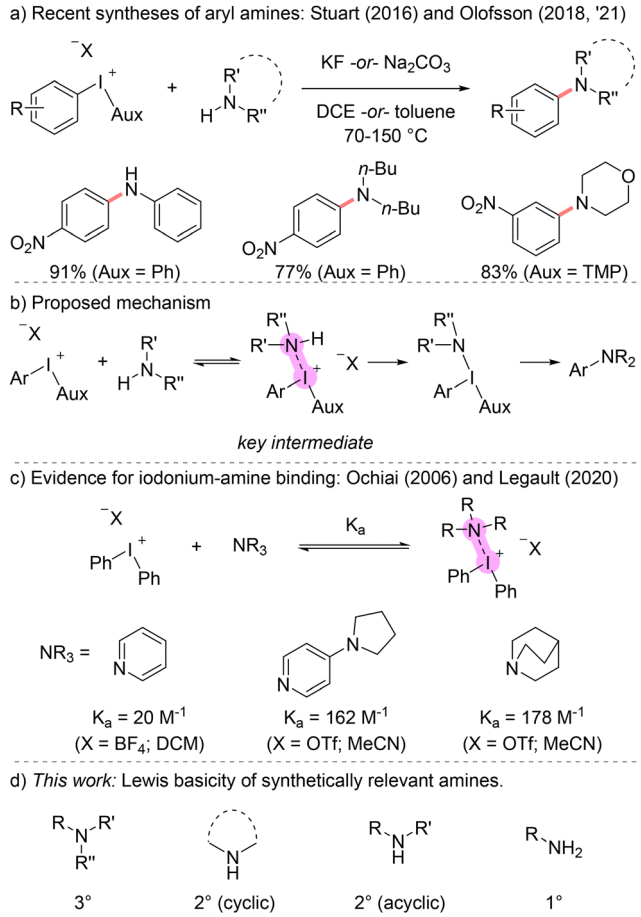


Scheme 1 Relevance and evidence of iodonium–amine binding.

The sensitivity, s_I, values obtained by this method (*i.e.*, the slope of the correlations) ranged from 0.68–0.78 and were similar to that previously reported for quinuclidine (0.85).[10] Moreover, the LB_I value obtained in this work for DABCO was 2.24, which is very similar to the LB_I value of 2.25 for structurally related quinuclidine (Fig. 2).[10] The LB_I values calculated for secondary and primary amines were less than that of tertiary DABCO (Fig. 2). Acyclic secondary and primary amines, **8** and **9**, followed DABCO with LB_I values of 2.09 and 1.97, respectively (Fig. 2). We found that secondary cyclic amines, piperidine **6** and morpholine 7, were less Lewis basic than acyclic amines on the Legault iodonium Lewis acidity scale (Fig. 2). We found that the aromatic amine, aniline **10**, had a Lewis basicity of 1.76, which is between that of piperidine and morpholine (Fig. 2). The correlation of observed and calculated log K_a values obtained in this study overlay well with the model developed by Legault based on eqn (1) (see Fig. S2 in the ESI†). However, the LB_I values obtained for amines **5–10** did not correlate well with other empirically determined parameters for amines, such as pK_a of the conjugate acid or Mayr nucleophilicity (N) (see Fig. S3 in the ESI†).[11–14]

In addition to diphenyliodonium, unsymmetrical aryl(TMP)-iodonium and aryl(DMIX)iodonium reagents have been used in metal-free C–N coupling reactions.[3,4,8] The electron-rich TMP and DMIX dummy ligands promote chemoselective aryl transfer of the other aryl group to amine nucleophiles. Legault has previously reported the LA_I value for phenyl(TMP)iodonium hexafluorophosphate salt as −0.38, and suggests that the weaker Lewis acidity relative to diphenyliodonium is due to the electron-rich TMP group.[10] We used five of the amines **5–9** studied here as reference

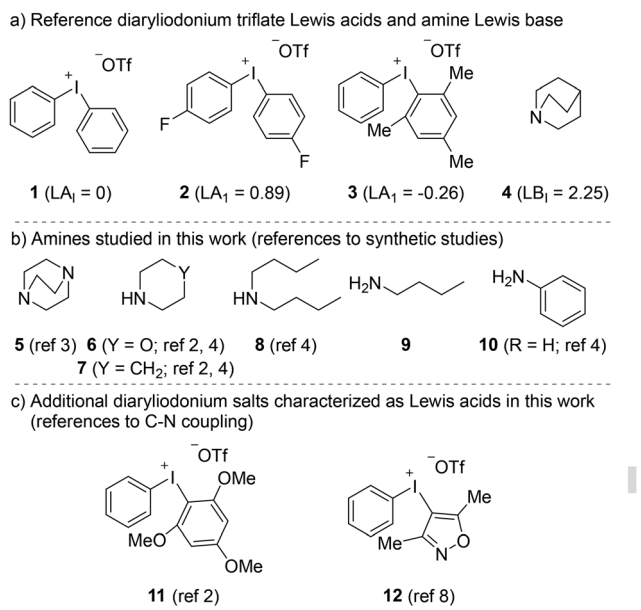
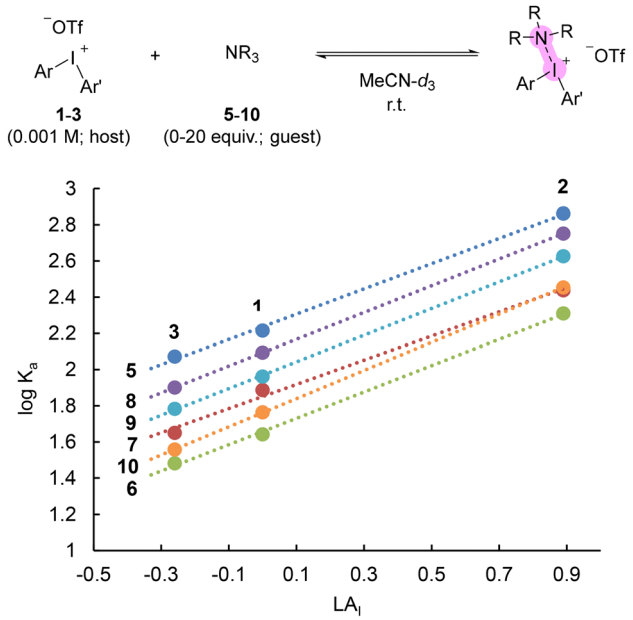


Fig. 1 Diaryliodonium salts and amines used in this work.



Entry	Amine	s_I	LB_I
1	**5** (DABCO)	0.70	2.24
2	**6** (morpholine)	0.73	1.66
3	**7** (piperidine)	0.68	1.84
4	**8** (dibutyl amine)	0.74	2.09
5	**9** (butyl amine)	0.74	1.97
6	**10** (aniline)	0.78	1.76

Fig. 2 Correlation of log K_a with LA_I for diaryliodoniums **1–3** and amines **5–10**.

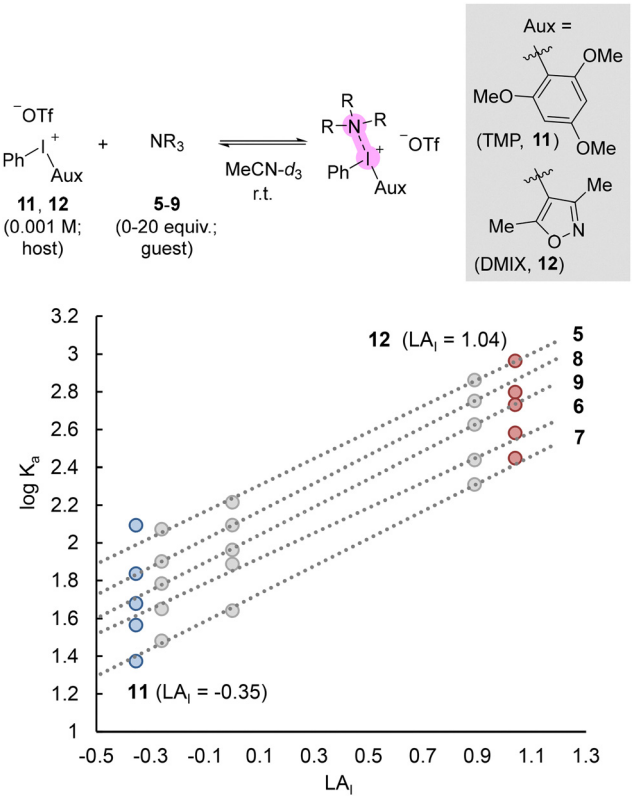
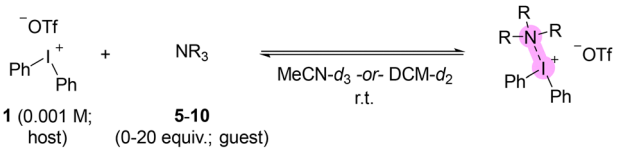


Fig. 3 Determination of LA_I for unsymmetrical diaryliodoniums **11** and **12**. (Grey data points are from Fig. 2.)

Lewis bases to determine the LA_I values for phenyl(TMP)-iodonium and phenyl(DMIX)iodonium triflate salts **11** and **12** (Fig. 3). Based on these experiments and least square linear regression fitting of the data, we obtained an LA_I value of −0.35 for **11** with the TMP auxiliary (Fig. 3, blue data points), similar to the value previously obtained by Legault for the corresponding hexafluorophosphate salt.[10] However, we were somewhat surprised to find that phenyl(DMIX)iodonium triflate **12** had substantially higher K_a values with all of the amines used as reference Lewis bases and a resulting LA_I value of 1.04 (Fig. 3, orange data points). Structurally, the phenyl(DMIX)iodonium **12** and phenyl(Mes)iodonium **3** both have aryl ligands with two *ortho*-positioned methyl groups, but have very different LA_I values (LA_I of **12** = 1.04 and LA_I of **3** = −0.26). A closer inspection of both steric and electronic effects might reveal a cause for this discrepancy. First, X-ray structure data for a related DMIX compound and **3** reveal C–I bond distances of 2.06 and 2.10 Å, respectively.[8,15] However, the 5-membered ring of DMIX actually positions the methyl groups further away from iodine than the 6-membered ring of Mes (3.68 *vs.* 3.27 Å, respectively) and therefore the DMIX ligand is less sterically encumbering than Mes. Second, the 5-membered imidazole ring of DMIX is inductively withdrawing, whereas the Mes group is inductively donating, and therefore the iodonium of **12** is more electron-deficient than **3**.[16]

Although, the Legault iodonium Lewis acidity scale was developed using acetonitrile as the solvent, dichloroethane and toluene are used more commonly in C–N coupling



K_a (MeCN-d_3): **5** > **8** > **9** > **7** > **10** > **6**
K_a (DCM-d_2): **9** > **5** > **8** > **7** > **6** > **10**

Entry	Amine	K_a (MeCN-d_3) M^{-1}	K_a (DCM-d_2) M^{-1}
1	**5** (DABCO)	1.64×10^2	1.40×10^2
2	**6** (morpholine)	4.38×10^1	9.68×10^0
3	**7** (piperidine)	7.16×10^1	5.78×10^1
4	**8** (dibutyl amine)	1.24×10^2	6.75×10^1
5	**9** (butyl amine)	9.16×10^1	1.69×10^2
6	**10** (aniline)	5.81×10^1	1.54×10^0

Fig. 4 Comparison of K_a values in MeCN-d_3 and DCM-d_2.

reactions with diaryliodonium salts,[4,6,7] though DMF is also used for aniline arylation.[2,3,8] We performed ^{1}H NMR titration experiments with diphenyliodonium triflate **1** and amines **5–10** in dichloromethane-d_2 to test the solvent effects on the association of amines with diphenyliodonium triflate. In prior work, Legault observed that association constants for diphenyliodonium and benzoate increase with decreasing solvent polarity,[10,17] which is consistent with weaker ion stabilization in less polar solvent and therefore a greater extent of ion-pairing (association) between iodonium and benzoate. Here, we observed that in almost all cases the observed association constants between diphenyliodonium and neutral amines were smaller in magnitude in DCM-d_2 than in MeCN-d_3 (Fig. 4), which is in contrast to Legault's observation with anionic benzoate. Our rationale for this result is that in DCM-d_2, which is less polar than MeCN,[17] there is a greater extent of ion-pairing between diphenyliodonium and triflate which attenuates the Lewis acidity of diphenyliodonium group; this trend holds for K_a values obtained in acetone-d_6, which has polarity between DCM and acetonitrile (see Fig. S5, in the ESI†). However, it is important to note that the trend in K_a values for the amines was not consistent between the two solvents and may reflect other phenomena taking place during these interactions. For instance, primary butylamine had the highest K_a value (1.69×10^2 M^{-1}) in DCM-d_2, but the third highest (K_a = 9.16×10^1 M^{-1}) in MeCN-d_3 (Fig. 4). The order of K_a values, from largest to smallest, is **5** > **8** > **7** > **6** was consistent in both solvents. However, aniline **10** had a higher K_a value than morpholine in MeCN-d_3 (*cf.* 58.1 *vs.* 43.8 M^{-1}), but morpholine had the higher value in DCM-d_2 (Fig. 4, entries 2 and 6).

In conclusion, we have determined the Lewis basicity values for six synthetically relevant amines (**5–10**) on the Legault Lewis acidity scale, including representative tertiary, secondary, and primary amines, aliphatic and aromatic, as well as cyclic and acyclic amines. In the course of these studies, we also determined the Lewis acidity of two unsymmetrical diaryliodonium salts (**11** and **12**) that have been used in metal-free C–N coupling reactions. Finally, we found that binding events between iodonium and neutral amines generally have smaller association constants in less polar solvent, which is opposite to the observed trend for anionic Lewis bases.

Conceptualization – SB, SJ, and DRS; investigation and methodology – SJ, SB, MB; supervision – SB and DRS; writing (original draft) – DRS; writing (reviewing and editing) – SJ, SB, DRS; funding acquisition, validation, project administration, and resources – DRS.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of ESI.†

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