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Examination of Pyridazine as a Possible Scaffold for Nucleophilic Catalysis

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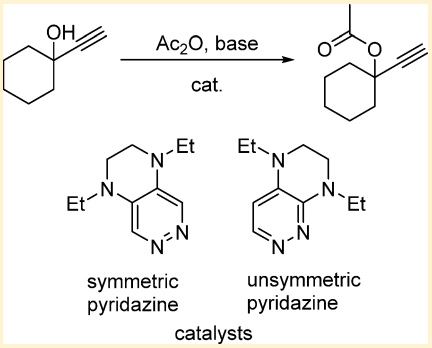
Supporting Information

ABSTRACT: Pyridazines with amino groups positioned para to each aromatic ring nitrogen and fixed in six-membered rings were prepared. The representative symmetric amino *N*-Et derivative was found to slightly exceed DMAP in catalytic activity in the acetylation reaction of a tertiary alcohol in C_6D_6. Nucleophilicity eclipsing that of DMAP was established in competitive reactions using phenacyl bromide as the electrophile, and the unsymmetric *N*-Et derivative was revealed to have even higher nucleophilicity.



INTRODUCTION

The highly nucleophilic derivative of pyridine (**1**), 4-dimethylaminopyridine (DMAP, **2**), has been the most widely used nucleophilic catalyst for the acylation reaction (Figure 1) due to its efficiency, versatility, and availability.[1−3] The more reactive 4-pyrrolidinopyridine (PPY, **3**) has been found to get the job done is some cases where DMAP failed.[4] The mechanism of the catalytic cycle with acetic anhydride has been established experimentally[2e,3b,5] and theoretically[6] to be as shown in Figure 2, involving a fast pre-equilibrium between the catalyst and the active acyl intermediate (the first step) and an ensuing rate-limiting reaction between this intermediate and

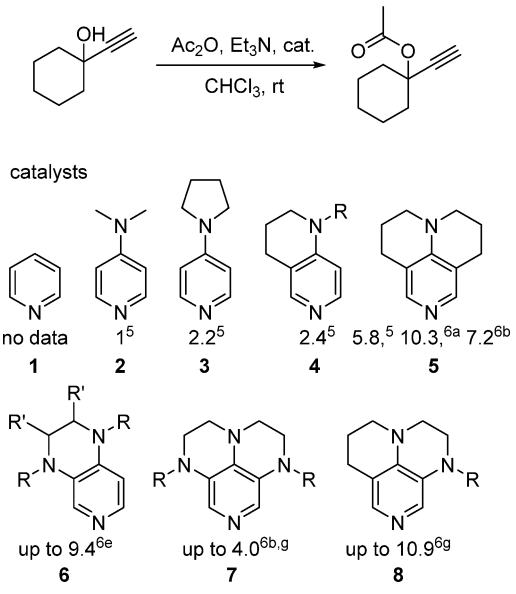


Figure 1. Benchmark acetylation reaction and pyridine derivatives examined as nucleophilic catalysts. The values correspond to reactivity relative to that of DMAP.

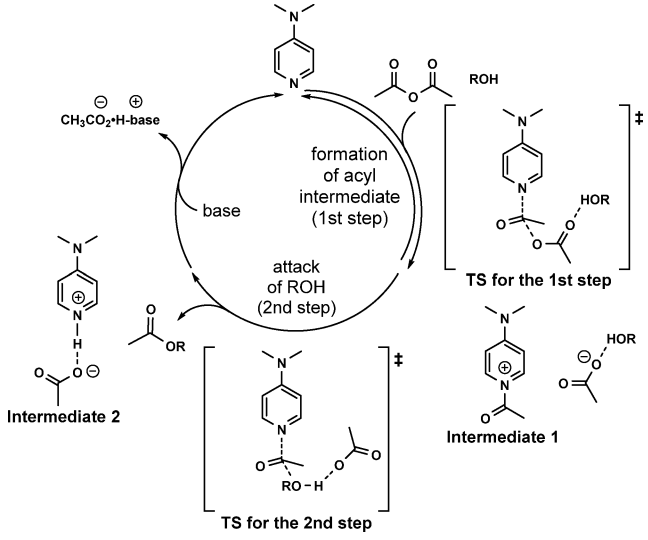


Figure 2. Proposed mechanism for the catalytic cycle for acylation with DMAP.

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the substrate alcohol (the second step) as the key processes.[2e,14,15] Tetrahedral intermediates can be imagined to form immediately after the reaction between the catalyst and the anhydride and that between the acyl intermediate and the substrate alcohol. However, these intermediates are extremely short-lived if they exist at all,[15] and thus it is not unreasonable to omit them as meaningful intermediates in the catalytic cycle.

After the discovery of PPY, it was long assumed that the improvement of pyridine based nucleophilic catalysts had hit a peak. It took some 30 years for the emergence of the seminal report by Steglich, Mayr, Zipse, and co-workers to manifest that catalytic activity could actually be improved, by fixing the *para*-amino group nitrogen atom into a fused system in the form of two-ringed **4** and three-ringed **5**, with the latter excelling in reactivity among the two.[7] Since then, in addition to fixation, the addition of extra amino groups has also been examined.[6] The substitution of the methylene group directly attached to the pyridine ring in **4** has given **6**,[8a,b,e,f] and two or one similar substitutions in **5** have given **7**[8b,d,g] or **8**,[8g] respectively. The underlying idea here for the design of the new catalysts was to increase nucleophilicity and basicity, which would be important for facilitating the first step involving the formation of the active acyl intermediate and for increasing the effective concentration of this important intermediate. The catalytic activity of these compounds has been evaluated and compared using the benchmark reaction (Figure 1), which involves the acetylation of a lowly reactive tertiary alcohol, and it has been found that all of these polycyclic frameworks have provided compounds that have catalytic activity exceeding that of DMAP. However, here again it seems that a ceiling has been reached, suggesting that some different platform might be required for further improvement. Although catalytic efficiency is naturally dependent on the identity of the reaction type examined, for the acylation reaction, a comprehensive analysis of the reported data implies that the addition of two fused six-membered rings as in **5** and **8** is favorable for raising activity, while adding a third amino group as in **7** might not necessarily be so, even though nucleophilicity is expected to rise. The reversal of catalytic activity contrary to the magnitude of nucleophilicity between **5** and **7** (R = Et)[8c,g] suggests that the electrophilicity of the carbonyl carbon of the acetylated intermediate in the ester forming second step has a strong influence on the overall outcome of the multistep catalytic process. Thus, for the optimum catalyst, both nucleophilicity and electronegativity, which may conflict, have to be considered, though it may be difficult to quantify the effect of the two.

We have had an ongoing interest in the use of pyridine derivatives and cinchona alkaloids as reagents and catalysts[9] and had been wondering whether some other scaffold could be used for nucleophilic catalysis. Hassner reported in the acetylation reaction of a lowly reactive tertiary alcohol that 4-pyrrolidinopyridazine **10b**, a supposedly highly nucleophilic derivative of **9**, was completely ineffective.[10] Probably for this reason, the pyridazine core has been completely ignored as a possible catalyst framework. The cause of the low activity can be attributed to the strong electron-withdrawing inductive property (element electronegativity) of the nitrogen atom adjacent to the catalytic reaction site, which would be detrimental to nucleophilic activity. However, the pyridazine framework seemed to be attractive for examination, since it could be envisioned that the in-plane alignment of the lone pairs of the adjacent nitrogen atoms might lead to a positive α-effect type activation.[11] In fact, it has been mentioned earlier that the recombination of the lone pair orbitals on the two nitrogen atoms takes place to form a bonding and an antibonding orbital and that the presence of the occupied antibonding orbital is relevant for explaining the unique bathochromic shift of the n−π^* UV absorption of pyridazine **9** relative to those of isomeric pyrazine and pyrimidine.[12] This spectroscopic feature in turn implied the rise in the HOMO, which is of nitrogen lone-pair nature, and the possibility of the aforementioned α-effect. To raise the potential of compound **10b**, it seemed legitimate to apply the logic for the pyridine system by introducing an amino group *para* to the other aromatic nitrogen atom and fixing the two amino groups in a ring as in **11** (Figure 3).[8] Since a resonance structure can be

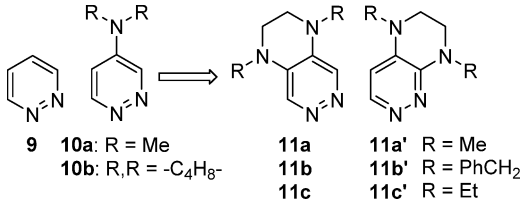

Figure 3. Pyridazine derivatives as candidates for nucleophilic catalysts.

drawn in which the amino group *meta* to the activating site could donate electrons to the nitrogen atom neighboring the active site nitrogen atom, it was anticipated that this additional amino group would have a stronger activation effect compared with the pyridine system where the effect of the amino group *meta* to the reaction site is more of a inductive type one with only a weak electron-donor effect (σ_m = +0.16).[13] Thus, it was speculated that the extra electron density donated by a *meta*-amino group via a resonance effect could work to largely reduce the negative inductive effect of the nitrogen atom neighboring the active site nitrogen and also to increase the nitrogen lone pair antibonding HOMO energy level. Along with the planned ring fixation, these effects were expected to function in synergy to improve catalytic activity. As will be described, theoretical calculations that were initially carried out provided support for our working hypothesis. Based upon these results, we embarked on a study on the designed pyridazine derivatives. Herein are the details.

RESULTS AND DISCUSSION

Examination of several synthetic routes that seemingly would give the target product selectively proved to be unsuccessful, and therefore we resorted to a route involving a literature procedure that would give the precursor to the target product as an isomeric mixture (Scheme 1). As found during the subsequential examination of compound properties (vide infra), this turned out to be in our favor. Thus, dichloromaleic anhydride was treated with hydrazine dihydrochloride to give 4,5-dichloro-6-hydroxypyridazin-3(2*H*)-one (**13**) in 95% yield.[14] NMR suggested an unsymmetric structure for this compound. Substitution of the hydroxy groups with chlorines was achieved with phosphoryl chloride to give **14** in 40% yield.[15] Reaction of tetrachloropyridazine with N^1,N^2-bis-(phenylmethyl)-1,2-ethanediamine gave a mixture of symmetric **15b** and unsymmetric **15b′** in the ratio of 3:1.[16] Mixtures of **15a** and **15a′**, and **15c** and **15c′** were obtained with similar ratios. For the methyl and phenylmethyl mixtures, isomer separation was carried out at this stage, whereas for the ethyl

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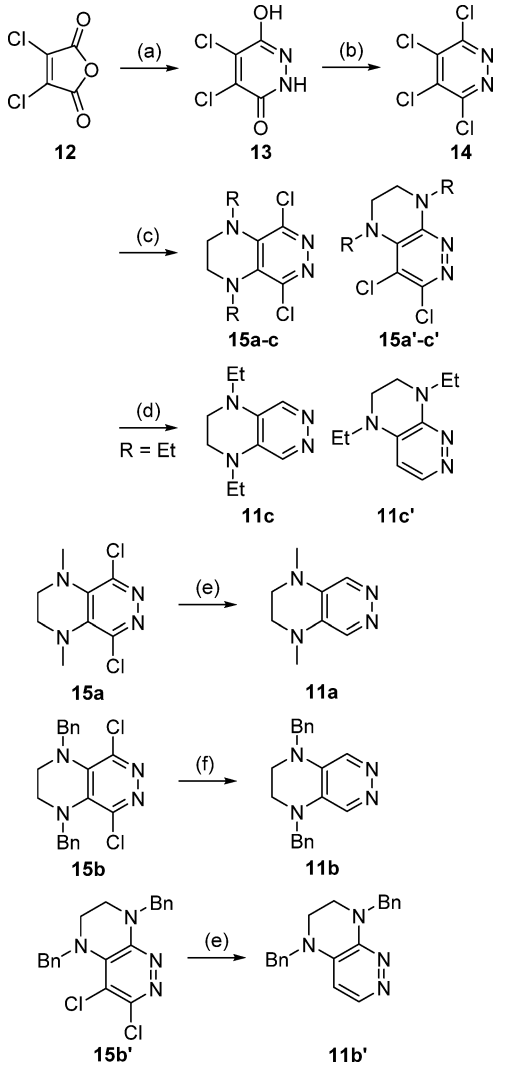
Scheme 1. Synthesis of the Pyridazine Derivatives[a]



[a]Reagents and conditions: (a) N_2H_4−2HCl, H_2O, reflux, 1 h, 95%; (b) $POCl_3$, reflux, overnight, 40%; (c) $RNHCH_2CH_2NHR$ (R = Me, Bn, Et), Et_3N, DMF, or MeCN, rt, overnight, **15a** = 58%, **15b**/**15b′** = 46%:15%; (d) H_2, 10% Pd−C, Et_3N, EtOH, 70 °C, overnight, **11c**/**11c′** = 28%:24% over 2 steps; (e) H_2, 10% Pd−C, Et_3N, EtOH, rt, overnight, **11a** = 61%, **11b′** = 92%; (f) $LiAlH_4$, THF, 0 °C, 2.5 h, 46%.

derivatives, the mixture was carried over to the next reaction. For the subsequent reduction to the target products, hydrogenation using Pd on carbon was sufficient except for **15b**. In this case, probably due to steric hindrance, the hydrogenation process was very sluggish and prolonged reaction times led to mixtures including not only the partially reduced product with one chlorine remaining but also some other unidentified side-products. Thus, for **15b**, we resorted to $LiAlH_4$ reduction. Even for this alternative method, careful monitoring was required to avoid over-reduction. Although the most reactive unsymmetric ethyl derivative **11c′** (vide infra) was found to gradually decompose upon standing, the solid symmetric derivatives (**11b** and **11c**) were found to be quite stable. This is in contrast to compounds with core structures of pyridine, which have been reported to require careful purification due to their susceptibility to oxidation.[8g]

In order to determine the viability of our working hypothesis, theoretical calculations were carried out. Cation affinities, which are thermodynamic parameters based on theoretical calculations proposed by Zipse,[17] have been found to exhibit high correlation with nucleophilicity,[8f,g] which is a kinetic property that can be determined experimentally.[18] Thus, we decided to make evaluations with this criterion. Since the rate-determining step in the acylation reaction catalyzed by DMAP has been established to be the second step involving the acyl-intermediate (Figure 1), the effective concentration of this intermediate was considered to be very important for high reactivity, and thus the use of acetyl affinity, one of the proposed cation affinity scales,[17] was deemed rational for making predictions. To this end, methyl substituted **11a** was selected as the model compound, and calculations were conducted at the RB3LYP/6-31G(d) and RMP2/6-31G(d) levels.[19] For the purpose of comparison, related derivatives of pyridine and pyridazine were also structurally optimized, along with unsymmetric **11a′**, obtained due to the synthetic route used. The calculated enthalpy differences of isodesmic reactions for acetylation with pyridine as the reference (eq 1) are given in Table 1. Although the level of theory is lower than those reported,[8a,b,f,g] there is a relatively good agreement with reported values of a slightly higher level of computation.[8a,b] Thus, we reasoned that our calculations should do for a qualitative assessment. Since positively charged species were involved, calculations based on the IEFPCM solvation model (benzene and chloroform) were also carried out. The DFT calculations gave optimized structures with slightly lower total energies compared with those by RMP2 (Table S1, Supporting Information), but as a whole, the two methods gave similar results for the isodesmic reactions. For the acetyl derivatives, pyridazine derivatives **11a**-**Ac**$^+$ and **11a′**-**Ac**$^+$ were found to be more stable than **6a**-**Ac**$^+$, the intermediate for **6a**, which is known to be more active than DMAP. This was regardless of the method of calculation used or whether solvation was considered, although the energy difference decreased with increasing solvent polarity. This is mainly due to the large difference in the degree of solvation among specific charged species. The unsymmetric pyridazine derivative **11a′**-**Ac**$^+$ was found to be slightly more stable than its symmetric counterpart. These findings were very inspiring for the utilization of the synthesized compounds. For the optimized acyl intermediates of the electron-rich pyridazines, the conformers with the carbonyl oxygen oriented anti (*s-trans*) to the adjacent nitrogen atom in the aromatic ring were clearly more stable than the other ones (*s-cis*), as evident from the values in parentheses. This is presumably because unfavorable repulsion between the lone-pair of this nitrogen atom and the lone-pairs of the carbonyl oxygen is minimized. The data in the table also shows that the effect of one amino group is much larger than the addition of a second amino group for enhancing the stability of the acyl intermediate relative to pyridine (ca. 60 to ca. 15−20 kJ/mol). A point of concern was that a comparison of values for **2**-**Ac**$^+$ and **10a**-**Ac**$^+$ suggested that Hassner's **10b** was more nucleophilic than DMAP, which contradicted experimental reactivity in the acylation reaction. Still so, since the difference in acetyl affinity with **2**-**Ac**$^+$ was much larger in our case, we were optimistic with our designed pyridazine derivatives.

Since HOMOs could be considered to be related to nucleophilicity, molecular orbitals were next inspected (Figure 4). DFT MOs are generally less reliable than HF MOs in an absolute sense but have been known to be applicable for relative comparisons.[20] In our case, in addition to large differences in absolute energy values, a change in the order of

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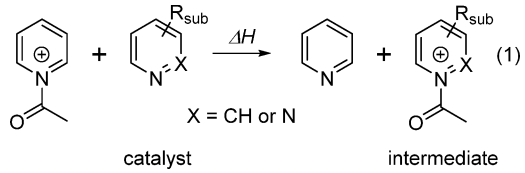
Table 1. Calculated Reaction Enthalpies for Acetyl Group Transfer (kJ/mol)[a]



catalyst/intermediate	level of theory	gas phase	C_6H_6 (ε = 2.247)[b]	$CHCl_3$ (ε = 4.9)[b]
2/2-Ac$^+$	RB3LYP-6-31G(d)	−82.8 ⟨−82.1⟩[d]	−63.7	−60.5
	RMP2-6-31G(d)	−79.6	−65.5	−58.7
6a[c]**/6a-Ac$^+$**[c]	RB3LYP-6-31G(d)	−105.8 ⟨−105⟩[d] (−109.0)[e]	−80.6 (−82.6)[e]	−74.5 (−75.9)[e]
	RMP2-6-31G(d)	−99.8 (−103.3)[e]	−78.7 (−80.7)[e]	−68.9 (−70.0)[e]
11a/11a-Ac$^+$	RB3LYP-6-31G(d)	−120.3 (−85.4)[e]	−88.1 (−59.0)[e]	−78.1 (−53.3)[e]
	RMP2-6-31G(d)	−117.8 (−81.9)[e]	−88.9 (−59.8)[e]	−74.7 (−49.7)[e]
11a′/11a′-Ac	RB3LYP-6-31G(d)	−121.6 (−96.5)[e]	−93.3 (−70.7)[e]	−85.3 (−65.0)[e]
	RMP2-6-31G(d)[c]	−121.8 (−97.0)[e]	−96.5 (−73.7)[e]	−77.1 (−56.3)[e]
10/10-Ac$^+$	RB3LYP-6-31G(d)	−91.5 (−61.3)[e]	−73.3 (−48.8)[e]	−67.7 (−46.9)[e]
	RMP2-6-31G(d)	−87.2 (−56.7)[e]	−67.4 (−42.4)[e]	−58.7 (−37.0)[e]
9/9-Ac$^+$	RB3LYP-6-31G(d)	−4.0 (26.1)[e]	3.7 (28.9)[e]	2.2 (23.9)[e]
	RMP2-6-31G(d)	−5.2 (23.4)[e]	−2.2 (22.9)[e]	0.4 (22.4)[e]

[a]For acetylated intermediates where conformational isomers are possible, the values are for the *s-trans* conformer. [b]Calculated using the IEFPCM solvation model. [c]R = Me, R′ = H for **6** in Figure 1. [d]Reported values from calculations at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.[8a] [e]Values for the *s-cis* conformer.

the MOs (Tables S2 and S3, Supporting Information) was found for all but **6a**. Using a larger basis set in B3LYP/cc-pVTZ lead to a slight lowering of total energies. However, there were essentially no differences in the MO profiles. Solvation also had little effect on the energy levels. Thus, the MOs based upon the RMP2 method were considered for qualitative analysis. For all of the compounds, the HOMO was of π-type, and orbitals corresponding to the nitrogen lone pairs were HOMO−2 orbitals with additional lower HOMOs for pyridazine derivatives. Thus, although we take it for granted that the formation of the acyl-intermediates involves in-plane attack of the nitrogen lone pair to the electrophile, the lone pairs actually do not constitute the highest HOMO. For all of the pyridazines, a large separation of the nitrogen lone pair bonding and antibonding orbital levels was found, and the higher antibonding orbital level was found to be slightly higher than that of the nitrogen lone pair orbital of the corresponding pyridine. For the series of pyridazine derivatives, there was a steady but small increase in this energy level on going from **9** to **10a** to **11a** and **11a′**. Interestingly, the energy gap between the two nitrogen lone pair based molecular orbitals did not differ much among these compounds except for **11a′**. This implies that the electron donation of the amino groups has little effect on this gap. On the other hand, the effect of amino substitution is substantial for the π-type orbitals, as the change in the HOMO and HOMO−1 energy levels indicate. Similar trends can be observed for the pyridine series (**1**, **2**,[21] and **6a**). The large difference in the effects of the amino groups on the π-type orbitals and the nitrogen lone pair based orbitals is reasonable considering the orthogonal relationship between the two groups of orbitals. Judging from the reported relative reactivity of the pyridine derivatives and the nucleophilic reactivity examined here for pyridazines (vide infra), there seems to be a better correlation between acetyl affinity and HOMO energy than between acetyl affinity and the energy levels of the nitrogen lone-pair based orbitals.

As for UV (Supporting Information), the weak long wavelength absorption for pyridazine **2** identified as n to π^* excitation [340 nm in both C_6H_{12} (ε = 315)[12b] and C_6H_{14} (ε = ca. 400)[22]] was speculated to no longer be observable explicitly for the newly prepared pyridazines **11c** and **11c′**, judging from the energy levels in the MO diagram in Figure 4. In fact, for symmetric **11c** (Figure S6, dotted line), an intense absorption was observed at 316 nm (CH_2Cl_2, extinction coefficient ε = 7180, log ε = 3.86) with a shoulder around 360 nm (CH_2Cl_2, ε = 710, log ε = 2.9), and for unsymmetric **11c′** (Figure S6, normal line), strong absorptions were observed at 284 nm (CH_2Cl_2, ε = 5090, log ε = 3.71) and 321 nm (CH_2Cl_2, ε = 4700, log ε = 3.67). The strong intensities suggested that the transitions were of π−π^* type,[23] as similarly observed at 260 nm ($CHCl_3$) for DMAP,[24] and TD-DFT calculations at the RB3LYP/6-31G(d) level of theory added support for these assignments. Thus, it is highly suggested that the HOMOs of pyridazines **11c** and **11c′** are indeed of π-type.

The basicities of the newly prepared compounds were examined by preparing camphorsulfonic acid salts of DMAP (**2-CSA**)[25] and pyridazines **11c** and **11c'** (**11c-CSA** and **11c'-CSA**). The acid was selected to ensure solubility of the salts for the equilibration measurements and because it is reasonably acidic. For the **11c** system, it was found that the addition of a large excess of the acid to **11c-CSA** did not change the NMR spectra of the monoacid salt. Therefore, despite of the possible electron-donation from the *para* amino group to the unprotonated nitrogen of **11c-CSA**, the basicity of this cationic species to give the doubly protonated form seems to be quite weak. Thus, to expect the association of the substrate alcohol to the acylated intermediate to increase reaction rate seemed to be out of the question. The symmetric nature of the pyridazine part of the NMR spectra of **11c-CSA** suggests that there is fast proton exchange between the two pyridazine ring nitrogen atoms.

pK_a approximations of the conjugated acids were conducted by determining the equilibrium ratio of a mixture originating from neutral **11c** or **11c'** and protonated **2-CSA**. The presence of a fast proton exchange process between the bases and their conjugated acids disabled the observation of the pairs as

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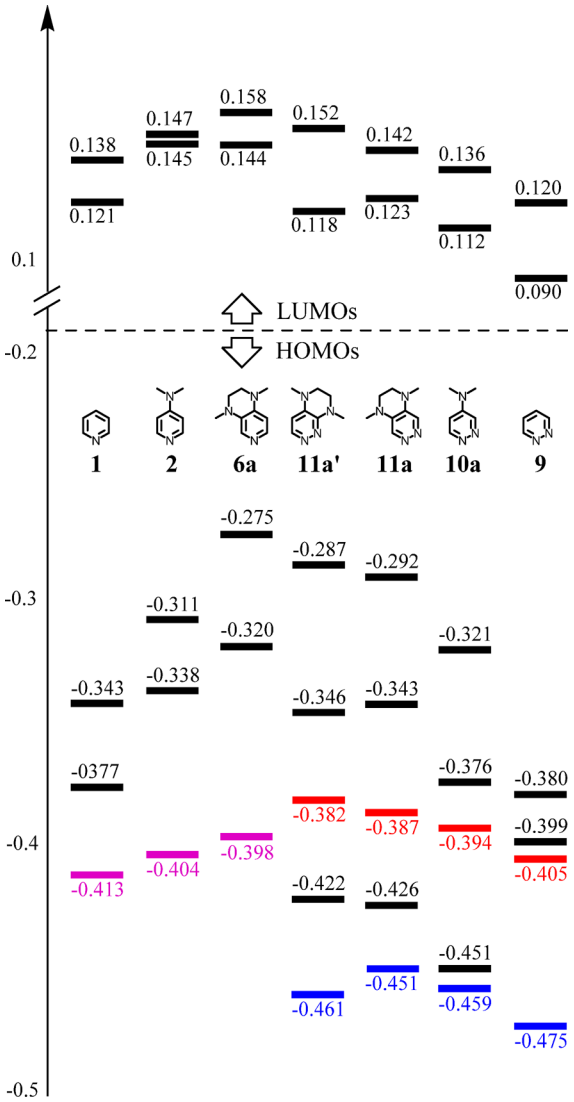
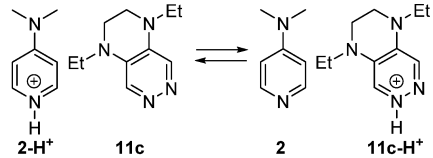


Figure 4. Energy levels of the molecular orbitals of pyridine and pyridazine derivatives calculated at the RMP2/6-31G(d) level of theory. The levels correspond to LUMO+1 down to HOMO−2, HOMO−3 or HOMO−4 from top to bottom. As for the colors of the levels and values, black, purple, blue, and red denote π-type orbitals, nitrogen lone pair orbitals, nitrogen lone pair bonding combination orbitals, and nitrogen lone pair antibonding combination orbitals, respectively.

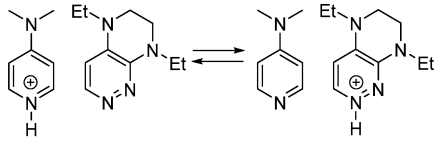
separate entities on the NMR time scale, and thus the NMR chemical shift interpolation method was adopted. To this end, known amounts of **2-CSA** and **11c** were mixed in dry CD_3CN, and the ratio of **2-CSA** and **2** was determined by interpolating the observed ^{13}C NMR chemical shift value of the aromatic 2-carbon between those of pure **2-CSA** and **2** (Scheme 2).[26] The calculated pK_a difference was 0.82 (see the experimental section, eq 2), indicating that there is nearly a one order difference with higher basicity for DMAP over **11c**. A similar analysis for **11c′** (Scheme 3) gave a difference of 0.14 (see experimental section), this time with higher basicity for **11c′**. As the pK_a differences show, unsymmetric **11c′** is more basic than **11c** by 0.96 in pK_a units. Using the scale by Leito for MeCN as the solvent, the pK_a values of the conjugated acids of **11c** and **11c′** would be 17.1 (MeCN) and 18.1 (MeCN), respectively,[27] from the value of 17.95 of the conjugated acid of DMAP.

Scheme 2. Equilibration of a Mixture of 2-CSA and 11c To Determine the Basicity of 11c



	2-H$^+$	**11c**	**2**	**11c-H$^+$**
initial ratio	100	99	0	0
at equilibrium	72.1	71.1	27.9	27.9

Scheme 3. Equilibration of a Mixture of 2-CSA and 11c′ To Determine the Basicity of 11c′



	2-H$^+$	**11c′**	**2**	**11c′-H$^+$**
initial ratio	100	105	0	0
at equilibrium	44.2	49.2	53.8	55.8

Though the solvent used for measurements was not the same, this difference in pK_a is again a good reproduction of what was observed between conjugated acids of symmetric 4,5-diaminopyridazine (pK_a = 9.0, H_2O) and unsymmetric 3,4-diaminopyridazine (pK_a = 10.0, H_2O).[23] The higher basicity for **11c′** compared with **11c** is in good agreement with the additional resonance structure possible for this species with negative charges on both pyridazine ring nitrogen atoms (Figure S2). Thus, although nucleophilicity is expected to be higher for our pyridazines compared with DMAP, basicity is actually a bit lower for symmetric **11c** and about the same for unsymmetric **11c′**.

Rate measurements of the acetylation reaction of 1-ethynylcyclohexan-1-ol, a tertiary alcohol, with our catalysts and DMAP were next carried out. In order to ensure constant temperature with our NMR instrument, rate measurements were carried out at 35 °C in $CDCl_3$, which has been a commonly used solvent for rate measurements. To simplify analysis of NMR spectra, *N*-methyl-2,2,6,6-tetramethylpiperidine (PMP), which has similar basicity to Et_3N but has no interfering signals, was used. Other bases with simple spectra such as tris(phenylmethyl)amine and 1,8-diazabicyclo[2.2.2]-octane (DABCO) were found to be unsuitable since they led to reduction of rate, probably because of reduced basicity for the former and competing nucleophilicity to give a lowly productive intermediate for the latter. The reason is not clear, but proton sponge bis-1,8-(dimethylamino)naphthalene, which supposedly has high basicity and low nucleophilicity, was also found to reduce the rate. The reaction profiles of our pyridazine derivatives along with that of DMAP are plotted in Figure 5. It is unfortunately evident that the catalytic activity of all of the pyridazines was inferior to that of DMAP. In terms of the time required for conversion to a common percentage, it took **11a** and **11b** about 9 times, **11b′** about 3.5 times, and **11c** and **11c′** about 3 times longer than DMAP. Thus, the catalytic activity of the pyridazine derivatives was not as high as we had expected. Nonetheless, we were able to show here that the pyridazine system is not completely inert for catalysis as previously thought.[10] A comparison among pyridazine derivatives shows that there was only a slight substituent effect concerning the amino group substituents, with the *N*-Et

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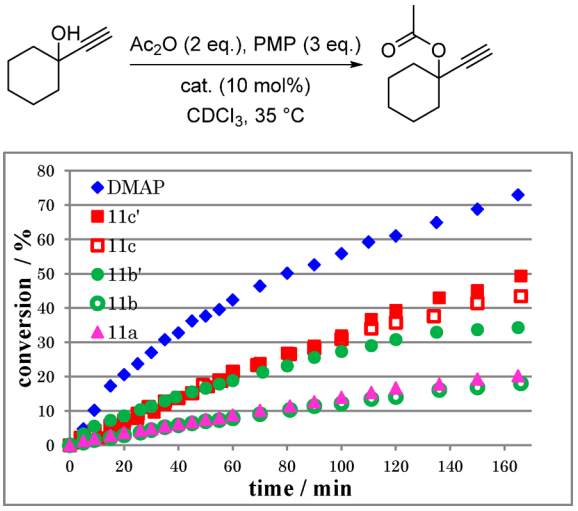

Figure 5. Rate measurements of acetylation in $CDCl_3$.

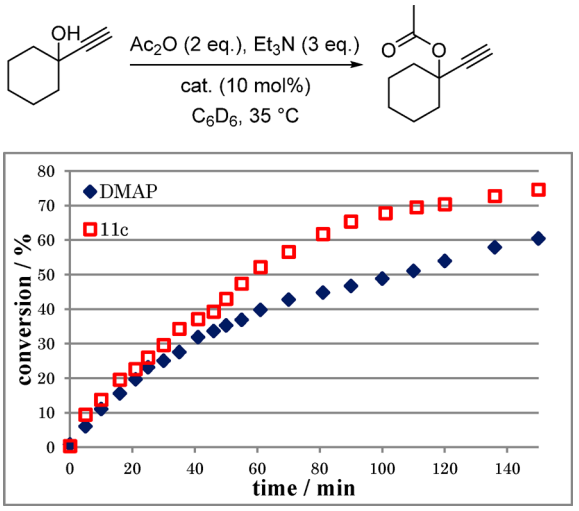

Figure 6. Rate measurements of acetylation in C_6D_6.

derivatives being somewhat more active than the others. For the phenylmethyl pair, the unsymmetric pyridazine **11b′** was obviously more reactive while there was practically no difference between the two *N*-Et derivatives. As for the difference in activity between the *N*-Me and N-Et derivatives, organic solvent affinity (hydrophobicity), which is directly related to the stability of the polar acetylated intermediate in organic solvents, might be operative. In the examination of alkyl chain length of the alkyl groups of the amino group of 4-aminopyridine derivatives by Zipse, a steady increase in reactivity was observed up to butyl substitution. Since the electron-donating inductive effect is not expected to increase much even with the ethyl group,[5] it is reasonable to interpret this result as a hydrophobicity effect. Thus, the higher activity of the *N*-Et derivatives can also be attributed to the higher solvent affinity of their acyl intermediates compared with their *N*-Me counterparts.

Preliminary measurements of reactions free of auxiliary base using **11b** as the catalyst were found to be even more sluggish than those using other bases examined above, as expected. Even in this case, a comparison of initial conversion showed DMAP to be at least 3 times more reactive than **11b**. Therefore, it seems reasonable to say that preassociation of the alcohol substrate to the free nitrogen atom of the acyl intermediate is negligible, in accordance with the low thermodynamic basicity of the monoprotonated pyridazine (vide supra).

From theoretical calculations, the large disagreement in catalytic activity between that expected from theory and that observed experimentally was reasoned to be due to the solvent polarity of chloroform, since the relative stabilities of **11a-Ac**$^+$ and **11a′-Ac**$^+$ over **6a-Ac**$^+$ were computed to be higher in less polar benzene than in chloroform (Table 1). Thus, we next examined the reaction using C_6D_6 instead of $CDCl_3$, with symmetric **11c**, which is the easier isomer to use. As the result shows (Figure 6), **11c** was found to be ca. 1.8 times as active as DMAP by a comparison at 50% conversion. Thus, although the magnitude is very small, one of our pyridazines was actually able to surpass DMAP in reactivity.

In order to determine the reason for the low catalytic activity, comparisons of nucleophilicity of our pyridazines with DMAP were carried out. For the electrophile, phenacyl bromide was chosen since its reaction was found to be reasonably fast, proceeding to completion within only a few hours, and because the phenacyl group is an electron-withdrawing group, though relatively weak.[28] As for authentic samples, single crystals of **11c-phen** were obtained and were crystallographically analyzed. The ORTEP drawing of one of three independent molecules is shown in Figure 7. A comparison of corresponding bonds in

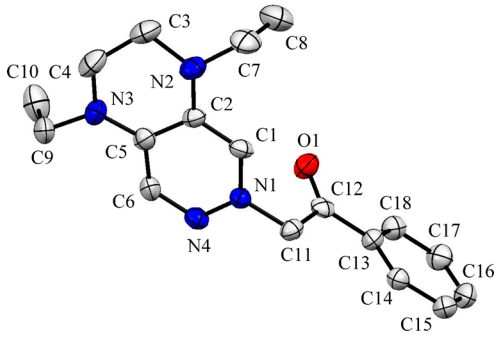

Figure 7. ORTEP drawing of one of three independent molecules of **11c-phen**$^+$ shown with thermal ellipsoids at the 50% probability level. Hydrogen atoms and the bromide (counteranion) have been omitted for clarity. Differences in structural parameters of all three molecules were practically within margin of error. Selected bond distances [Å] and angles [deg] for the depicted molecule: N(1)−N(4) 1.332(7), N(1)−C(1) 1.346(8), N(1)−C(11) 1.462(8), C(1)−C(2) 1.368(9), N(2)−C(2) 1.363(8), C(2)−C(5) 1.425(9), N(3)−C(5) 1.348(8), N(4)−C(6) 1.329(8), C(5)−C(6) 1.413(9), N(4)−N(1)−C(1) 124.6(5), N(4)−N(1)−C(11) 114.6(5), C(1)−N(1)−C(11) 120.3(5), N(1)−C(1)−C(2) 120.9(6), C(2)−N(2)−C(3) 116.8(6), C(2)−N(2)−C(7) 119.1(6), C(3)−N(2)−C(7) 117.3(6), N(2)−C(2)−C(1) 122.8(6), N(2)−C(2)−C(5) 120.1(6), C(1)−C(2)−C(5) 117.1(6), C(5)−N(3)−C(9) 123.1(6), C(5)−N(3)−C(4) 119.6(6), C(9)−N(3)−C(4) 117.2(6), N(2)−C(3)−C(4) 111.8(6), C(6)−N(4)−N(1) 116.1(5), N(3)−C(4)−C(3) 111.0(6), N(3)−C(5)−C(6) 122.8(6), N(3)−C(5)−C(2) 120.7(6), C(6)−C(5)−C(2) 116.5(6), N(4)−C(6)−C(5) 124.4(6).

the aromatic ring have N(1)−C(1) at 1.346(8) Å and N(4)−C(6) at 1.329(8) Å, C(6)−C(5) at 1.413(9) Å and C(1)−C(2) at 1.368(9) Å, and C(2)−N(2) at 1.363(8) Å and C(5)−N(3) at 1.346(8) Å. The differences indicate that the respective shorter latter bonds of each pair have higher double bond character, which in turn suggests high contribution of a resonance structure with no formal charge on the alkylated

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nitrogen atom (Figure S3, **11c-phen-C**). Furthermore, the three angle sum around N(3) is 359.9° indicating complete sp^2 hybridization, required for maximum electron donation. On the other hand, the corresponding value for the other amino group nitrogen N(2) is only 353.2°, thereby implying less efficient electron donation. This is understandable, since the aromatic nitrogen that has this nonplanar nitrogen atom positioned *para* is neutral and thus does not require resonance-type stabilization. The same three angle sum around the onium nitrogen is 355.3°, also a bit off complete planarity. The N(4)−N(2)−C(11) angle is 114.6(5)°, showing an inclination toward the neighboring electronegative nitrogen atom. The value of 1.425(9) Å for C(2)−C(5) is larger than that of C(6)−C(5) and that of the corresponding bond (1.375 Å by microwave spectroscopy[29]) in unsubstituted pyridazine **9**, which is considered to have high **11c-phen-B** type contribution. This in turn suggests that the C(2)−C(5) bond has high single bond character and thus that **11c-phen** has high contribution from **11c-phen-A**. The reason for this contrast in structure could be due to ring strain of the alicyclic ring and electrostatic repulsion of the two neighboring nitrogen atoms in **11c-phen**. Since the supposed active intermediate in the pyridazine catalyzed acetylation reaction is a similar pyridazinium cation, the electronic properties assumed from resonance structure contributions found here for **11c-phen** are expected to resemble those of the reaction intermediate. Thus, amino group electron-donation must indeed be crucial for the stabilization of the active intermediate, more so since the acetyl group is strongly electron-withdrawing as opposed to the weak corresponding effect of the phenacyl group here. For the record, intermolecular face-to-face π-stacking can be observed between the pyridazine ring and the phenacyl phenyl group in the unit cell, which are incidentally in a nearly perpendicular relationship within each molecule.

For **11c′-phen**, although the expected regioisomer would be the one depicted (Figure 8) on the grounds of steric hindrance,

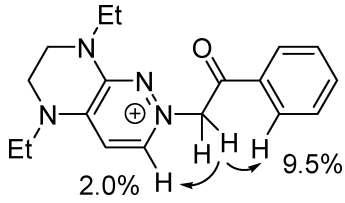
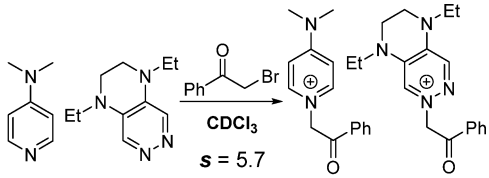


Figure 8. NOE intensity enhancements for **11c′-phen**$^+$.

this assignment was affirmed by difference NOE experiments. Irradiation of the methylene signal (δ = 6.61) resulted in intensity enhancements of 2.0% for the pyridazine 6-hydrogen signal (δ = 9.95) and 9.5% for that of the *ortho* hydrogen of the phenyl ring (δ = 8.06). The small value for the former suggests that the on average, the methylene hydrogens are not directly facing the 6-hydrogen in solution, while the methylene carbon and the phenyl ring are probably coplanar. Although solution and solid structures may differ, the ORTEP structure for **11c-phen**$^+$ (Figure 7) may be a good indication of its solution structure.

For approximations of nucleophilic reactivity, we decided to carry out straightforward and operationally simple competitive reactions.[18] Since, an exactly 1:1 molecular ratio of the compounds corresponds to a racemic mixture of reactants in kinetic resolutions, we figured that the approximate equation used to elucidate relative initial rates (selectivity factor *s*, eq 3 in the Experimental Section) could be applied here.[30] The competitive reactions were carried out at rt with $CDCl_3$, the same solvent as that used for the first acetylation reactions. It was independently confirmed that the alkylated heterocycles themselves do not act as alkylating agents and transfer the alkyl group to other heterocyclic molecules on the same reaction time scale. The reaction with symmetric **11c** gave *s* = 5.7 in favor of **11c** (Scheme 4). Therefore, as initially anticipated, our

Scheme 4. Competitive Nucleophilic Reaction between DMAP and Symmetric 11c in $CDCl_3$

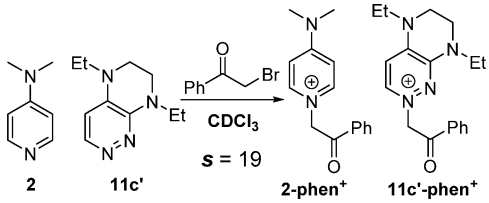


	2	11c	2-phen$^+$	11c-phen$^+$
initial ratio	50	50	0	0
end ratio	46.2	30.8	3.8	19.2

designed pyridazine is more nucleophilic than DMAP. Since basicity has been determined to be higher for DMAP (vide supra), it could be justified that for symmetric **11c**, the α-effect is actually operative.

Unsymmetric **11c′** gave rise to even a larger value of *s* = 19 (Scheme 5), in line with the difference in basicity favoring **11c′**

Scheme 5. Competitive Nucleophilic Reaction between DMAP and Symmetric 11c′ in $CDCl_3$

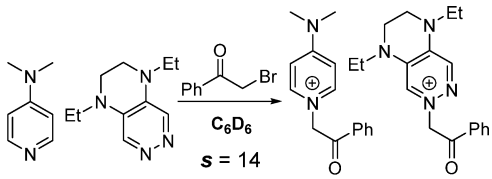


	2	11c′	2-phen$^+$	11c′-phen$^+$
initial ratio	50	50	0	0
end ratio	46.1	10.7	3.9	39.3

(vide supra). Thus, the extra resonance structure (Figure S2) for **11c′** seems to be an important difference maker. Owing to this large *s* value, we believe it is appropriate to say that the α-effect is also operative for unsymmetric **11c′**, relative to DMAP.

For benzene, which turned out to reverse catalytic reactivity in our favor, a comparison of nucleophilicity with symmetric **11c** resulted in a selectivity factor of *s* = 14 (Scheme 6). This difference is not quite as high as that (*s* = 19) for unsymmetric

Scheme 6. Competitive Nucleophilic Reaction between DMAP and Symmetric 11c in C_6D_6



	2	11c	2-phen$^+$	11c-phen$^+$
initial ratio	50	50	0	0
end ratio	45.5	13.8	4.5	36.4

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11c′ in $CDCl_3$, but surely higher than that of itself in $CDCl_3$ (s = 5.7). From these results, it could be concluded that the low polarity of the solvent helped to raise both nucleophilicity and catalytic activity of our pyridazines in the acylation reaction relative to DMAP.

The fact that the difference in nucleophilicity between the Et-*N* pyridazines and DMAP, which can be considered to be an indirect experimental indication of the difference in cation affinity, was not reflected in the acetylation reaction to the full suggests that the latter process of the catalytic cycle involving ester formation and regeneration of the catalyst is slower for our catalysts compared with DMAP (Figure 1).[3b] Considering the fact that it would be unfavorable to produce a species with obvious lone pair repulsion (free pyridazine), inevitable with our catalysts, the observed difference in reactivity of the second process is understandable. In addition, since the preferred conformation for the acylpyridazinium intermediate is the one where the carbonyl oxygen and the free nitrogen atom of the pyridazine ring are in an antiperiplanar relationship, a slight repulsive effect could be operative between the oxygen atom of the incoming alcohol and the adjacent unbonded free nitrogen atom during the attack of the alcohol to the carbonyl group (Figure 9). The fact that catalytic activities of symmetric **11c**

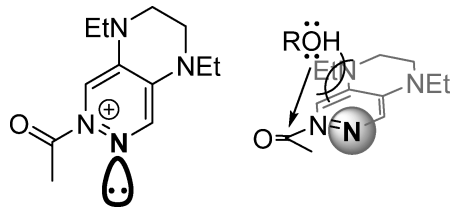

Figure 9. Image of the repulsive interaction plausible upon attack of the alcohol onto the active intermediate.

and unsymmetric **11c′** were about the same while nucleophilicity clearly favored **11c′** implies that this ester formation step is slower for unsymmetric **11c′**. This serves as a good example of higher electron density (**11c′**) having contradicting effects, the positive higher nucleophilicity of the catalyst and the negative lower carbonyl reactivity of the intermediate.

CONCLUSION

In conclusion, we have examined the possibility of using the pyridazine scaffold for nucleophilic catalysis and have found that one of our novel pyridazines with amino groups in the 3,4-positions fixed in a six-membered ring (**11c**) can actually exceed DMAP in catalytic activity, though moderately, in the acetylation reaction of a tertiary alcohol in C_6D_6, a solvent of low polarity. Thus, it can be said that there is an efficient trade-off between the inductive effect of the endocyclic extra aromatic nitrogen of the pyridazine core, which reduces nucleophilicity, and the electron-donating effect of the exocyclic (in terms of the pyridazine ring) extra amino group, which raises it. Examination of nucleophilicity showed that the pyridazine derivatives are undoubtedly more nucleophilic that DMAP with the unsymmetric derivative **11c′** showing higher nucleophilicity. The low mutual relationship between catalytic activity and nucleophilicity suggested that the reactivity of the acylpyridazinium intermediates were lower than that of the corresponding DMAP intermediate, and a rationale for the cause has been presented. As for the order of basicity, it was unsymmetric **11c′** > DMAP > symmetric **11c**. So for the pyridazines, unsymmetric **11c′** is both more nucleophilic and more basic than symmetric **11c**, and a comparison with DMAP suggests small α-effects are operative for these compounds. Although we could not fulfill our objective to the full, our catalysts should be effective for application to reactions that require high nucleophilicity of the catalyst and stability of the catalyst adduct, and where the lone pair of the free nitrogen atom of the adduct does not interfere in ensuing reactions.[31] Also, due to their high Lewis basicity and structural feature of having adjacent nitrogen atoms, our compounds may serve as signature ligands for metal complexes.[32] Efforts in these areas are currently underway.

EXPERIMENTAL SECTION

Materials and Methods. All reagents were used without further purification unless noted otherwise. All solvents were distilled prior to use using conventional methods. N^1,N^2-bis(phenylmethyl)-1,2-diaminoethane,[33] 4-(dimethylamino)pyridin-1-ium, ((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate (**2-CSA**),[25] and 4-(dimethylamino)-1-(2-oxo-2-phenylethyl)pyridin-1-ium bromide (**2-phen**$^+$)[27] were prepared according to literature procedures. Melting points are uncorrected. ^{1}H and ^{13}C spectra were recorded on a 400 or a 500 MHz spectrometer. ^{1}H and ^{13}C chemical shifts were referenced to the internal deuterated solvent or its residue (^{1}H δ 7.26, ^{13}C δ 77.2 for $CDCl_3$; ^{1}H δ 2.50, ^{13}C δ 39.5 for DMSO-d_6; ^{1}H δ 1.94, ^{13}C δ 118.3 for CD_3CN; ^{1}H δ 7.16, ^{13}C δ 128.1 for C_6D_6). ^{13}C NMR multiplicities were determined with the DEPT mode. IR spectra were measured by placing samples between KRS-5 plates. High resolution mass spectra were measured in either the ESI or APCI mode on an ion trap mass analyzer. Column chromatography was performed with silica gel (N60) or basic alumina (90). Thin-layer chromatography was performed on plates precoated with silica gel or basic alumina containing F_{254} for UV visualization.

*4,5-Dichloro-6-hydroxypyridazin-3(2H)-one (**13**).*[14] To a mixture of water (28 mL) and hydrazine dihydrochloride salt (6.31 g, 60.1 mmol), dichloromandelic anhydride (10.0 g, 60.1 mmol) was added portionwise, and the resulting solution was stirred at rt for 2 h. The solution was then brought to reflux and was stirred for another hour. After this time, the solution was cooled to rt, and the solid that precipitated out was collected by filtration to give the title compound **13** (10 g, 95% yield) as a white solid. Spectroscopic data suggests that the compound exists in an unsymmetric form. Mp 295.5−296.0 °C (lit. 296 °C, decomp),[14] sublimes at 270 °C. R_f = 0.25 (MeOH/CH_2Cl_2 = 1:3). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.6 (br s, 1H), 12.2 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 155.4 (C), 149.6 (C), 135.7 (C), 131.2 (C).

*Tetrachloropyridazine (**14**).*[15] A solution of 4,5-dichloro-6-hydroxypyridazin-3(2*H*)-one **13** (0.99 g, 5.5 mmol) in 11 mL (120 mmol) of freshly distilled $POCl_3$ was stirred at reflux overnight. The excess $POCl_3$ was distilled off by evaporation. The residue was poured onto cracked ice and then made alkaline with concentrated aqueous ammonium hydroxide. The crude product was collected by filtration of the alkaline mixture and purified by recrystallization (hot EtOH) to afford **14** (0.47 g, 2.2 mmol, 40%) as white crystals. Mp 83.0−84.0 °C (lit. 85−86 °C).[15a] R_f = 0.70 (AcOEt/hexane = 4:1). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (C), 137.0 (C).

*1,4-Bis(phenylmethyl)-5,8-dichloro-1,2,3,4-tetrahydropyrazino-[2,3-d]pyridazine (**15b**) and 5,8-Bis(phenylmethyl)-3,4-dichloro-5,6,7,8-tetrahydropyrazino[2,3-c]pyridazine (**15b′**).* Tetrachloropyridazine (0.21 g, 0.98 mmol) was dissolved in DMF (16 mL) under argon with stirring. To it, a solution of N^1,N^2-bis(phenylmethyl)-1,2-diamine (0.25 g, 1.1 mmol) and Et_3N (0.38 mL, 2.8 mmol) in DMF (2 mL) was added, and the resulting mixture was stirred at rt for 28 h. The reaction mixture was concentrated under reduced pressure. The residue was made alkaline with Na_2CO_3 aq and extracted with AcOEt. The combined organic extracts were dried over Na_2SO_4 and evaporated under vacuum, and the residue was purified by silica gel column chromatography (AcOEt/CH_2Cl_2 = 1:25) to afford **15b** (0.17

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g, 0.45 mmol, 46%) as white crystals and **15b′** (58 mg, 0.15 mmol, 15%) as a pale yellow solid. 1,4-Bis(phenylmethyl)-5,8-dichloro-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (**15b**): Mp 189.0−191.5 °C; R_f = 0.29 (AcOEt/CH_2Cl_2 = 1:25). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47−7.31 (m, 10H), 4.43 (s, 4H), 2.89 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.0 (C), 136.1 (C), 136.0 (C), 128.4 (CH), 127.7 (CH), 127.7 (CH), 57.8 (CH_2), 42.4 (CH_2). IR: ν (cm^{-1}) 3086, 3052, 3032, 2914, 2871, 2846, 1606, 1585, 1529, 1506, 1466, 1450, 1441, 1392, 1357, 1319, 1300, 1238, 1188, 1157, 1117, 1072, 1028, 1014, 991, 975, 939, 928, 895, 845, 791, 750, 727, 694, 669, 631, 604, 559. HR-MS (ESI Positive): Calcd for $C_{20}H_{18}Cl_2N_4Na$ ([M + Na]$^+$) *m*/*z* 407.0794, found 407.0801. Anal. Calcd for $C_{20}H_{18}Cl_2N_4$: C, 62.35%; H, 4.71%; N, 14.54%. Found: C61.96%; H, 4.72%; N, 14.39%. 5,8-Bis(phenylmethyl)-3,4-dichloro-5,6,7,8-tetrahydropyrazino[2,3-*c*]-pyridazine (**15b′**): Mp 193.0−194.0 °C; R_f = 0.48 (AcOEt/CH_2Cl_2 = 1:25). ^{1}H NMR ($CDCl_3$) δ = 7.44−7.20 (m, 10H), 4.93 (s, 2H), 4.50 (s, 2H), 3.21−3.14 (m, 2H), 3.12−3.05 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 151.4 (C), 146.0 (C), 137.0 (C), 136.6 (C), 133.8 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 119.5 (C), 57.0 (CH_2), 52.0 (CH_2), 45.7 (CH_2), 42.3 (CH_2). IR: ν (cm^{-1}) 3087, 3059, 3028, 2933, 2850, 1603, 1585, 1550, 1508, 1452, 1363, 1321, 1288, 1279, 1250, 1215, 1178, 1144, 1128, 1078, 1065, 1028, 991, 930, 847, 806, 733, 700, 627, 600, 543. HR-MS (ESI Positive): Calcd for $C_{20}H_{19}Cl_2N_4$ ([M + H]$^+$) *m*/*z* 385.0981, found 385.0982.

*1,4-Bis(phenylmethyl)-1,2,3,4-tetrahydropyrazino[2,3-d]-pyridazine (**11b**).* A solution of 1,4-bis(phenylmethyl)-5,8-dichloro-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (0.54 g, 1.4 mmol) in dry THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.32 g, 8.5 mmol) in dry THF (25 mL) under N_2 at 0 °C. The mixture was stirred at 0 °C for 4 h. The excess $LiAlH_4$ was quenched with water and 15% NaOH aq at 0 °C. The reaction mixture was filtered, and the filtered solid was washed with 15% NaOH aq, followed by THF and Et_2O. The organic solvents were distilled off and then the residue was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and evaporated under vacuum, and the residue was purified by alumina column chromatography (MeOH/CH_2Cl_2 = 30:1) to afford **11b** (0.17 g, 0.45 mmol, 46%) as a pale yellow solid. Mp 154.0−157.0 °C; R_f = 0.26 (alumina, AcOEt/CH_2Cl_2 = 1:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (s, 2H), 7.39−7.23 (m, 10H), 4.53 (s, 4H), 3.47 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (CH), 134.3 (C), 131.9 (C), 129.1 (CH), 127.9 (CH), 127.2 (CH), 53.9 (CH_2), 46.4 (CH_2). IR: ν (cm^{-1}) 3028, 2926, 2858, 2349, 1560, 1495, 1452, 1408, 1352, 1279, 1244, 1228, 1201, 1136, 1082, 1070, 1028, 1003, 891, 866, 733, 700, 663. HR-MS (ESI Positive): Calcd for $C_{20}H_{21}N_4$ ([M + H]$^+$) *m*/*z* 317.1761, found 317.1765. Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.92%; H, 6.37%; N, 17.71%. Found: C, 75.71%; H, 6.16%; N, 17.65%.

*5,8-Bis(phenylmethyl)-5,6,7,8-tetrahydropyrazino[2,3-c]-pyridazine (**11b′**).* To a solution of 5,8-bis(phenylmethyl)-3,4-dichloro-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazine (0.21 g, 0.54 mmol) and 10% Pd/C (24 mg) in EtOH under H_2, Et_3N (0.20 mL, 1.4 mmol) was added at rt and stirred overnight. The reaction mixture was filtered through Celite and washed with hot EtOH. After removal of the solvent, $NaHCO_3$ aq was added, and then the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford **11b′** (0.16 mg, 0.50 mmol, 92%) as a pale yellow oil. R_f = 0.23 (alumina, MeOH/CH_2Cl_2 = 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 5.4 Hz, 1H), 7.42−7.20 (m, 8H), 7.22 (d, *J* = 7.0 Hz. 2H), 6.22 (d, *J* = 5.4 Hz, 1H), 5.01 (s, 2H), 4.48 (s, 2H), 3.46 (dd, *J* = 5.4, 4.3 Hz, 2H), 3.37 (dd, *J* = 5.4, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.0 (C), 144.2 (CH), 137.5 (CH), 135.4 (C), 134.3 (CH), 128.7 (CH), 128.3 (CH), 127.4 (CH), 127.0 (CH), 126.6 (CH), 102.4 (CH), 53.2 (CH_2), 51.0 (CH_2), 46.6 (CH_2), 43.2 (CH_2). IR: ν (cm^{-1}) 3062, 2920, 2870, 2364, 1639, 1601, 1570, 1529, 1496, 1454, 1358, 1300, 1257, 1180, 1161, 1119, 1084, 1030, 887, 810, 748, 702, 660, 613, 575. HR-MS (ESI Positive): Calcd for $C_{20}H_{21}N_4$ ([M + H]$^+$) *m*/*z* 317.1761, found 317.1765.

*5,8-Dichloro-1,4-dimethyl-1,2,3,4-tetrahydropyrazino[2,3-d]-pyridazine (**15a**).*[16] Tetrachloropyridazine (0.10 g, 0.46 mmol) was dissolved in CH_3CN (4 mL) under argon with stirring. To it a solution of N^1,N^2-dimethylethane-1,2-diamine (0.050 mL, 0.46 mmol) and Et_3N (0.19 mL, 1.4 mmol) in CH_3CN (2 mL) was added at 0 °C. The resulting mixture was stirred at the same temperature for 1 h and then it was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated by reduced pressure, and then it was made alkaline with Na_2CO_3 aq and extracted with AcOEt. The combined organic extracts were dried over Na_2SO_4 and evaporated under vacuum. Purification by silica gel column chromatography (AcOEt/CH_2Cl_2 = 1:1) afforded **15a** (62.9 mg, 0.27 mmol, 58%) as a white solid. Mp 149.0−150.5 °C (lit. 143.5−146 °C).[20] R_f = 0.53 (AcOEt/CH_2Cl_2 = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.07 (s, 4H), 3.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.2 (C),136.4 (C), 136.0 (C), 46.5 (CH_3), 43.3 (CH_2). IR: ν (cm^{-1}) 2924, 2877, 1516, 1493, 1458, 1419, 1404, 1362, 1331, 1308, 1242, 1215, 1138, 1115, 1076, 1038, 984, 891, 852, 810, 667, 621, 590, 540. HR-MS (APCI Positive): Calcd for $C_8H_{11}Cl_2N_4$ ([M + H]$^+$) *m*/*z* 233.0355, found 233.0357.

*1,4-Dimethyl-1,2,3,4-tetrahydropyrazino[2,3-d]pyridazine (**11a**).* To a solution of 5,8-dichloro-1,4-dimethyl-1,2,3,4-tetrahydropyrazino-[2,3-*d*]pyridazine (50 mg, 0.21 mmol) and 10% Pd/C in EtOH under H_2, Et_3N (0.090 mL, 0.63 mmol) was added at room temperature, and the resulting mixture was stirred overnight. The reaction mixture was then filtered through Celite and washed with hot EtOH. After removing the solvent, $NaHCO_3$ aq was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. Purification by alumina column chromatography (MeOH/CH_2Cl_2 = 1:40) afforded **11a** (21.8 mg, 0.13 mmol, 61%) as a pale yellow solid. Mp 132.0−134.5 °C; R_f = 0.31 (alumina, MeOH/CH_2Cl_2 = 1:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (s, 2H), 3.40 (s, 4H), 2.94 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.1 (CH), 132.9 (C), 40.4 (CH_3), 37.8 (CH_2). IR: ν (cm^{-1}) 2962, 2927, 1655, 1577, 1462, 1400, 1350, 1315, 1284, 1257, 1203, 1107, 1061, 1038, 899, 868, 798, 748, 640, 575. HR-MS (APCI Positive): Calcd for $C_8H_{13}N_4$ ([M + H]$^+$) *m*/*z* 165.1135, found 165.1132. Anal. Calcd for $C_8H_{12}N_4$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.72%; H, 7.50%; N, 33.75%.

*1,4-Diethyl-1,2,3,4-tetrahydropyrazino[2,3-d]pyridazine (**11c**) and 5,8-Diethyl-5,6,7,8-tetrahydropyrazino[2,3-c]pyridazine (**11c′**).* Tetrachloropyridazine (1.0 g, 4.6 mmol) was dissolved in CH_3CN (30 mL) under argon. To it, a solution of N^1,N^2-diethylethane-1,2-diamine (0.66 mL, 4.6 mmol) and Et_3N (1.9 mL, 14 mmol) in CH_3CN (20 mL) was added at 0 °C. The resulting mixture was stirred at same temperature for 1 h, and then it was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated by reduced pressure, and then it was made alkaline with Na_2CO_3 aq and extracted with AcOEt. The combined organic extracts were dried over Na_2SO_4 and evaporated under vacuum to give a crude mixture of 5,8-dichloro-1,4-diethyl-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (**15c**) and 3,4-dichloro-5,8-diethyl-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazine (**15c′**). To a solution of this crude product and 10% Pd/C in EtOH under H_2, Et_3N (1.6 mL, 12 mmol) was added at room temperature, and resulting mixture was stirred at 70 °C overnight. The reaction mixture was filtered through Celite and washed with hot EtOH. After removing the solvent, $NaHCO_3$ aq was added, and then the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. Purification by alumina column chromatography (MeOH/AcOEt = 1:10) afforded **11c** (250 mg, 1.3 mmol, 28%) as a pale yellow solid and **11c′** (210 mg, 1.1 mmol, 24%) as a pale yellow oil. 1,4-Diethyl-1,2,3,4-tetrahydropyrazino[2,3-*d*]-pyridazine (**11c**): Mp 97.0−98.0 °C; R_f = 0.20 (alumina, MeOH/AcOEt = 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 2H), 3.40 (s, 4H), 3.39 (q, *J* = 7.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8 (CH), 131.3 (C), 45.1 (CH_2), 44.3 (CH_2), 10.6 (CH_3). IR: ν (cm^{-1}) 2974, 2933, 2875, 1655, 1562, 1498, 1477, 1454, 1412, 1377, 1350, 1277, 1230, 1180, 1113, 1090, 1067, 1047, 1028, 949, 895, 870, 793, 777, 754, 723, 631, 613, 563, 503. HR-MS (APCI Positive): Calcd for $C_{10}H_{17}N_4$ ([M + H]$^+$) *m*/*z* 193.1448, found 193.1447. 5,8-Diethyl-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazine (**11c′**): R_f = 0.48 (alumina, MeOH/AcOEt = 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 5.5 Hz, 1H), 6.15 (d, *J* = 5.5 Hz, 1H), 3.73 (q, *J* = 7.1 Hz, 2H), 3.51−3.32 (m, 4H), 3.32 (q, *J* = 7.2 Hz, 4H),

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1.20 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9 (C), 143.8 (CH), 134.1 (CH), 101.5 (CH), 45.4 (CH_2), 44.2 (CH_2), 43.8 (CH_2), 43.3 (CH_2), 11.2 (CH_3), 10.1 (CH_3). IR: ν (cm^{-1}) 2974, 2933, 2871, 1581, 1550, 1500, 1458, 1373, 1356, 1281, 1190, 1132, 1092, 1063, 1043, 1025, 953, 889, 816, 779, 763, 694, 636, 607. HR-MS (APCI Positive): Calcd for $C_{10}H_{17}N_4$ ([M + H]$^+$) m/z 193.1448, found 193.1447.

*1,4-Diethyl-1,2,3,4-tetrahydropyrazino[2,3-d]pyridazin-6-ium ((1R,4R)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonate (**11c-CSA**).* To a solution of (+)-10-camphorsulfonic acid (24.2 mg, 0.10 mmol), 1,4-diethyl-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (20.0 mg, 0.10 mmol) was added at room temperature, and the resulting mixture was stirred for 1.5 h. The solvent was evaporated under vacuum to afford **11c-CSA** (44.5 mg, 0.10 mmol, quant.) as a pale yellow gummy solid. ^{1}H NMR (400 MHz, CD_3CN) δ = 8.22 (s, 2H), 3.51 (q, J = 7.3 Hz, 4H), 3.50 (s, 4H), 3.15 (d, J = 14.6 Hz, 1H), 2.69 (d, J = 15.1 Hz, 1H), 2.67 (dt, J = 3.8, 12.9 Hz, 1H), 2.28 (td, J = 3.9, 18.5 Hz, 1H), 2.02 (t, J = 4.6 Hz, 1H), 1.99−1.95 (m, 1H), 1.84 (t, J = 18.2 Hz, 1H), 1.55 (ddd, J = 4.8, 9.4, 14.2 Hz, 1H), 1.35 (ddd, J = 3.8, 9.3, 13.7 Hz, 1H), 1.18 (t, J = 7.1 Hz, 6H), 1.07 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ = 217.5 (C), 135.6 (br CH), 127.5 (br C), 59.2 (C), 48.4 (C), 47.9 (CH_2), 45.9 (CH_2), 45.2 (br CH_2), 43.5 (CH_3), 43.3 (CH_2), 27.5 (CH_2), 25.4 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 10.8 (CH_3). IR: ν (cm^{-1}) 3475(br), 2966, 2889, 1739, 1639, 1589, 1574, 1504, 1454, 1419, 1381, 1354, 1284, 1267, 1230, 1173, 1107, 1041, 964, 937, 895, 856, 791, 714, 617, 582, 534, 517. HR-MS (ESI Positive): Calcd for $C_{10}H_{17}N_4$ ([M + H]$^+$) m/z 193.1448, found 193.1447. HR-MS (ESI Negative): Calcd for $C_{10}H_{15}O_4S$ ([M − H]$^-$) m/z 231.0697, found 231.0695.

*5,8-Diethyl-5,6,7,8-tetrahydropyrazino[2,3-c]pyridazin-1-ium ((1R,4R)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonate (**11c′-CSA**).* To a solution of (+)-10-Camphorsulfonic acid (24.2 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL), 5,8-diethyl-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazine (20.0 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was added at room temperature, and the mixture was stirred for 4.5 h. The solvent was evaporated under vacuum to afford the desired **11c′-CSA** (46.7 mg, 0.10 mmol, quant.) as a pale yellow oil. ^{1}H NMR (400 MHz, CD_3CN) δ = 8.27 (d, J = 6.6 Hz, 1H), 6.61 (d, J = 6.8 Hz, 1H), 3.64−3.48 (m, 8H), 3.15 (d, J = 14.7 Hz, 1H), 2.67 (d, J = 14.7 Hz, 1H), 2.72−2.65 (m, 1H), 2.29 (td, J = 3.8, 12.1 Hz, 1H), 2.03−1.94 (m, 2H), 1.84 (d, J = 18.1 Hz, 1H), 1.55 (ddd, J = 4.1, 9.2, 13.8 Hz, 1H), 1.35 (ddd, J = 3.8, 8.5, 12.3 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), 1.09 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ = 217.3 (C), 148.1 (C), 140.7 (C), 138.0 (CH), 101.1 (CH), 59.2 (C), 48.3 (CH), 47.8 (CH_2), 46.8 (CH_2), 46.7 (CH_2), 44.4 (CH_2), 43.4 (CH_2), 43.3 (CH_2), 43.2 (CH_2). 27.5 (CH_2), 25.4 (CH_2), 20.3 (CH_3), 20.0 (CH_3), 10.8 (CH_3), 10.5 (CH_3). IR: ν (cm^{-1}) 3477(br), 2977, 2362, 2343, 1736, 1603, 1572, 1541, 1483, 1381, 1358, 1292, 1232, 1188, 1171, 1149, 1107, 1041, 962, 895, 816, 791, 683, 669, 617, 579, 557, 536, 511. HR-MS (ESI Positive): Calcd for $C_{10}H_{17}N_4$ ([M + H]$^+$) m/z 193.1448, found 193.1449. HR-MS (ESI Negative): Calcd for $C_{10}H_{15}O_4S$ ([M − H]$^-$) m/z 231.0697, found 231.0694.

*1,4-Diethyl-6-(2-oxo-2-phenylethyl)-1,2,3,4-tetrahydropyrazino-[2,3-d]pyridazin-6-ium Bromide (**11c-phen**$^+$).* A solution of 1,4-diethyl-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (5.2 mg, 0.027 mmol) and 2-bromo-1-phenylethan-1-one (5.3 mg, 0.026 mmol) in dry $CDCl_3$ was stirred at rt for 3 h. The solvent was evaporated under vacuum and then the crude product was washed with Et_2O to afford **11c-phen**$^+$ (13 mg, quant.) as a pale yellow solid. Single crystals suitable for X-ray analysis were obtained by recrystallization from hexane−CH_2Cl_2. Mp 109.0−114.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.55 (s, 1H), 8.06 (d, J = 8 Hz, 2H), 7.99 (s, 1H), 7.61 (t, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 2H), 6.61 (s, 2H), 3.67 (q, J = 7 Hz, 2H), 3.65 (t, J = 5 Hz, 2H), 3.61 (q, J = 7 Hz, 2H), 3.50 (t, J = 5 Hz, 2H), 1.31 (t, J = 7 Hz, 3H), 1.26 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.9 (C), 135.0 (C), 134.6 (CH), 134.1 (C), 133.9 (C), 130.0 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 67.9 (CH_2), 46.2 (CH_2), 46.0 (CH_2), 45.9 (CH_2), 43.4 (CH_2), 11.4 (CH_3), 10.9 (CH_3). IR: ν (cm^{-1}) 3043, 2978, 2931, 2364, 2333, 1697, 1597, 1574, 1520, 1450, 1431, 1381, 1350, 1292, 1231, 1219, 1165, 1107, 1045, 1003, 906, 887, 849, 798, 764, 690, 667, 636, 598, 575, 505. HR-MS (ESI Positive): Calcd for $C_{18}H_{23}N_4O$ ([M]$^+$) m/z 311.1866, found 311.1868. MS (ESI Negative): Calcd for $^{79}Br^-$, m/z 79, found 79; $^{81}Br^-$, m/z 81, found 81.

*5,8-Diethyl-2-(2-oxo-2-phenylethyl)-5,6,7,8-tetrahydropyrazino-[2,3-c]pyridazin-2-ium Bromide (**11c′-phen**$^+$).* A solution of 5,8-diethyl-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazine (5.0 mg, 0.026 mmol) and 2-bromo-1-phenylethan-1-one (5.2 mg, 0.026 mmol) in dry $CDCl_3$ (0.6 mL) was stirred at rt for 4 h. The solvent was evaporated under vacuum, and then the crude product was washed with Et_2O to afford **11c′-phen**$^+$ (13 mg, quant.) as a pale yellow solid. Mp 250 °C (dec). ^{1}H NMR (100 MHz, $CDCl_3$) δ = 9.31 (d, J = 7 Hz, 1H), 8.07 (d, J = 7 Hz, 2H), 7.65 (t, J = 7 Hz, 1H), 7.53 (t, J = 7 Hz, 2H), 6.69 (d, J = 7 Hz, 1H), 6.37 (s, 2H), 3.71 (t, J = 5 Hz, 2H), 3.66−3.48 (m, 6H), 1.33 (t, J = 7 Hz, 3H), 1.15 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.5 (C), 146.7 (C), 142.4 (CH), 138.7 (C), 134.6 (CH), 134.1 (C), 129.2 (CH), 128.6 (CH), 101.9 (CH), 66.9 (CH_2), 46.8 (CH_2), 46.2 (CH_2), 44.5 (CH_2), 43.0 (CH_2), 10.8 (CH_3), 10.6 (CH_3). IR: ν (cm^{-1}) 2929, 2357, 1702, 1597, 1579, 1549, 1540, 1500, 1398, 1354, 1298, 1228, 1188, 1155, 1093, 1005, 769, 692, 661, 582, 517. HR-MS (ESI Positive): Calcd for $C_{18}H_{23}N_4O$ ([M]$^+$) m/z 311.1866, found 311.1868. MS (ESI Negative): Calcd for $^{79}Br^-$, m/z 79, found 79; $^{81}Br^-$, m/z 81, found 81.

Determination of the Acidity of the Conjugated Acids of 11c (11c-CSA) and 11c′ (11c′-CSA). *General Method, Symmetric **11c-H**$^+$.* The camphorsulfonic acid salt of DMAP (**2-CSA**, DMAP-CSA in eq 2)[25] (5.5 mg, 0.016 mmol) and 1,4-diethyl-1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazine (**11c**, 3.0 mg, 0.016 mmol, PZ for both isomers in the equation) were dissolved in dry CD_3CN (0.6 mL) in a NMR tube under a nitrogen atmosphere. To ensure complete dissolution, the tube was dipped in an ultrasonic wave bath for ca. 10 min, and then the tube was inserted into an NMR spectrometer. The ratio of DMAP and its CSA salt was calculated by interpolating the observed value using the ^{13}C NMR chemical shift values of pure DMAP and its CSA salt. That of PZ and its CSA salt was calculated from the ratio of the initial ratio of DMAP-CSA and PZ (100:99). Chemical shifts of the 2-carbon of pure DMAP and DMAP-CSA were δ 150.44 and 140.07, respectively. After mixing of DMAP-CSA and **11c**, the corresponding signal appeared at δ 142.96. Thus, [DMAP]/[DMAP-CSA] = 27.9:72.1, and in turn, [PZ]/[PZ-CSA] = 71.1:27.9.

$$\Delta pK_a = -\log \frac{K_{DMAP}}{K_{PZ}} = -\log \frac{[PZ\text{-}CSA]}{[PZ]} \frac{[DMAP]}{[DMAP\text{-}CSA]} = 0.82 \quad (2)$$

*Unsymmetric **11c′-H**$^+$.* An analogous analysis from the initial ratio of DMAP-CSA and PZ (100:105), and equilibrium ratios of [DMAP]/[DMAP-CSA] = 53.8:44.2 and [PZ]/[PZ-CSA] = 49.2:55.8 gave ΔpK_a = −0.14.

Rate Measurement Experiments. *Solution Preparation.* Stock solution A1: 1-Ethynylcyclohexan-1-ol (75 mg, 0.60 mmol) and PMP (0.33 mL, 1.8 mmol) were diluted with dry $CDCl_3$ in a 1 mL volumetric flask (1-ethynylcyclohexan-1-ol = 0.6 M; PMP = 1.8 M). Stock solution A2: 1-Ethynylcyclohexan-1-ol (0.15 g, 1.2 mmol) and PMP (0.65 mL, 3.6 mmol) were diluted with dry $CDCl_3$ in a 1 mL volumetric flask (1-ethynylcyclohexan-1-ol = 1.2 M; PMP = 3.6 M). Stock solution A3: 1-Ethynylcyclohexan-1-ol (50 mg, 0.40 mmol) and NEt_3 (0.17 mL, 1.2 mmol) were diluted with dry C_6D_6 in a 1 mL volumetric flask (1-ethynylcyclohexan-1-ol = 0.40 M, NEt_3 = 1.2 M). Stock solution B1: Acetic anhydride (0.11 mL, 1.2 mmol) was diluted with dry $CDCl_3$ in a 1 mL volumetric flask (1.2 M). Stock solution B2: Acetic anhydride (0.23 mL, 2.4 mmol) was diluted with dry $CDCl_3$ in a 1 mL volumetric flask (2.4 M). Stock solution B3: Acetic anhydride (0.23 mL, 2.4 mmol) was diluted with dry C_6D_6 in a 1 mL volumetric flask (2.4 M). Stock solution C1 (DMAP, Bn): Prepared by dissolving 0.060 mmol of each catalyst in dry $CDCl_3$ in a 1 mL volumetric flask and bringing the volume to the mark. Stock solution C2 (Me, Et): Prepared by dissolving 0.03 mmol of each catalyst in dry $CDCl_3$ in a 1 mL volumetric flask and bringing the volume to the mark. Stock

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solution C3 (Et): Prepared by dissolving 0.030 mmol of each catalyst in dry C_6D_6 in a 1 mL volumetric flask and bringing the volume to the mark.

*Rate Measurements. PMP as the Base, $CDCl_3$ as the Solvent, and DMAP or Bn (**11b**, **11b**′) Derivatives as the Catalyst.* Stock solution C1 of each catalyst (0.20 mL) was mixed with stock solution A1 (0.20 mL) in an NMR tube. Stock solution B1 (0.20 mL) was rapidly injected, and the tube was shaken to ensure complete mixing and immediately inserted into an NMR spectrometer. The conversion was measured by comparing the integrals of the peaks of 1-ethynylcyclohexan-1-ol (s, δ 2.37) and 1-ethynylcyclohexyl acetate ((s, δ 1.96) or (s, δ 2.52)). After the initial measurement, the conversion was checked at appropriate time intervals and plotted versus time. 1-Ethynylcyclohexan-1-ol = 0.20 M, Ac_2O = 0.40 M, PMP = 0.60 M, and catalyst = 0.020 M (1.0 mol %).

*PMP as the Base, $CDCl_3$ as the Solvent, and Me (**11a**) or Et (**11c**, **11c**′) Derivatives as the Catalyst.* Stock solution C2 of each catalyst (0.40 mL) was mixed with stock solution A2 (0.10 mL) in an NMR tube. Stock solution B2 (0.10 mL) was rapidly injected, and the tube was shaken to ensure complete mixing and immediately inserted into an NMR spectrometer. The conversion was measured by comparing the integrals of the peaks of 1-ethynylcyclohexan-1-ol (s, δ 2.37) and 1-ethynylcyclohexyl acetate ((s, δ 1.96) or (s, δ 2.52)). After the initial measurement, the conversion was checked at appropriate time intervals and plotted versus time. 1-Ethynylcyclohexan-1-ol = 0.20 M, Ac_2O = 0.40 M, PMP = 0.60 M, and catalyst = 0.020 M (1.0 mol %).

Et_3N as the Base and C_6D_6 as the Solvent. Stock solution C3 of each catalyst (0.20 mL) was mixed with stock solution A3 (0.30 mL) in an NMR tube. Stock solution B3 (0.10 mL) was rapidly injected, and the tube was shaken to ensure complete mixing and immediately inserted into an NMR spectrometer. The conversion was measured by comparing the integrals of the peaks of 1-ethynylcyclohexan-1-ol (s, δ 2.22) and 1-ethynylcyclohexyl acetate (s, δ 1.68). After the initial measurement, the conversion was checked at appropriate time intervals and plotted versus time. 1-Ethynylcyclohexan-1-ol = 0.20 M, Ac_2O = 0.40 M, PMP = 0.60 M, and catalyst = 0.020 M (1.0 mol %).

Competitive Nucleophilic Reactions Using Phenacyl Bromide as the Electrophile: General Method. DMAP (1.9 mg, 0.016 mmol) and **11c** or **11c**′ (3.0 mg, 0.016 mmol, PZ) were dissolved in dry $CDCl_3$ or C_6D_6 (0.6 mL) under a nitrogen atmosphere. After confirming the 1.0:1.0 ratio of DMAP and **11c** or **11c**′ by ^{1}H NMR, $PhCOCH_2Br$ (2.5 mg, 0.013 mmol) in dry $CDCl_3$ or C_6D_6 was added at rt. After about 2 h, ^{1}H NMR measurements were carried out, and the ratio of DMAP (reactant)/PZ (reactant)/DMAP−CH_2COPh (product)[28]/PZ-CH_2COPh (product) = $A/B/C/D$ was established. Reactant excesses (re), conversion ratios (C_r), and the selectivity factors (initial rate ratios, s) were calculated by eq 3 described below.[29]

$$\mathrm{re} = \frac{A-B}{A+B}, \quad C_r = \frac{C+D}{A+B+C+D}, \quad s = \frac{\ln(1-Cr)(1-\mathrm{re})}{\ln(1-Cr)(1+\mathrm{re})} \tag{3}$$

Computational Methods. Geometries were optimized at the RB3LYP/6-31G(d), RB3LYP/cc-pVTZ, and RMP2(FC)/6-31G(d) levels of theory using the Gaussian 09 Rev. D01 suite of programs. For solvation models (benzene and chloroform), the IEFPCM method was used. All minima were confirmed by the presence of only real vibrational frequencies. Zero-point energy corrections were scaled with a factor of 0.977, 0.985, and 0.964 for RB3LYP/6-31G(d), RB3LYP/cc-pVTZ, and RMP2(FC)/6-31G(d) calculations, respectively.[34] Thermal energies were not added to the total energies. TD-DFT calculations were carried out at the RB3LYP/6-31G(d) level of theory (td = (singlets, nstates =13, density = SCF)). Diagrams were generated with the GaussView program.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00630.

X-ray crystallographic data of compound **11c-phen**$^+$ (CIF)

Coordinates of theoretically calculated structures and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Prof. Kin-ya Akiba on the occasion of his 80th birthday.

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