OL Organic Letters

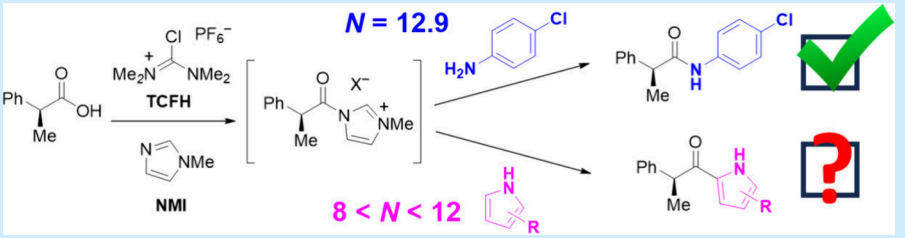
pubs.acs.org/OrgLett Letter

TCFH–NMI Ketone Synthesis Inspired by Nucleophilicity Scales

Johnson H. Ho, Grant H. Miller, Kasey K. Chung, Sydney D. Neibert, Gregory L. Beutner,* and David A. Vosburg*

Cite This: *Org. Lett.* 2024, 26, 8904–8909 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: *N,N,N′,N′*-Tetramethylchloroformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) enable the facile and practical reaction of carboxylic acids with amines, alcohols, and thiols to form amides, esters, and thioesters. To develop a mild synthesis of ketones with TCFH–NMI directly from carboxylic acids at room temperature, the Mayr nucleophilicity scale was used to compare the *N* values of competent nucleophiles to potential carbon-centered nucleophiles, identifying pyrroles and indoles as successful substrates when $N \geq 10$.

Mayr's scale of nucleophilicity and electrophilicity is a powerful concept in physical organic chemistry for explaining reactivity.[1] The scale uses kinetic data from the reactions of nucleophiles with reference electrophiles, or vice versa, to construct a simple mathematical relationship, allowing for an ordering of reactivity (eq 1). Substrates with larger *N* or *E* values on this logarithmic scale exhibit higher reaction rates ($k_{20°C}$). Comparing the parameters for two substrates in a known reaction allows chemists to understand why one substrate reacts quickly at room temperature, while another requires heating. But it can also be used to predict if some unprecedented pairing of nucleophile and electrophile will be successful, thereby guiding the development of novel reactions.[2] Over the past 30 years, the large reliable data set underpinning this scale has grown to >1500 examples representing a significant diversity of structures.[3] Further expansion of this broad scale is possible through application of computational models to predict the *N* and *E* values of substrates which have not been experimentally investigated.[4]

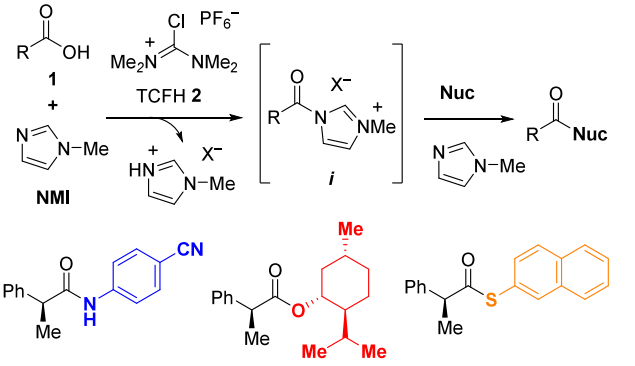
The Mayr–Patz Equation:

$$\log k_{20°C} = s_N(N + E) \quad (1)$$

s_N=nucleophile-specific sensitivity parameter
N=nucleophilicity parameter
E=electrophilicity parameter

The pairing of *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate (TCFH, **2**) and *N*-methylimidazole (NMI) has emerged as a practical reagent combination to access *N*-acyl imidazolium ions ***i***, highly electrophilic acyl donors which can be used to form amides, esters, and thioesters under mild conditions (Scheme 1).[5] Use of this reagent has gradually expanded to more heteroatomic nucleophiles including acyl hydrazides, hydroxylamines, and sulfonamides,[6] but no examples of ketone formation with carbon nucleophiles have been disclosed. To continue the exploration of TCFH–NMI as an alternative method of carboxylic acid activation versus acid chloride formation, which

Scheme 1. Reactions with TCFH–NMI



Received: September 8, 2024
Revised: October 1, 2024
Accepted: October 4, 2024
Published: October 7, 2024

https://doi.org/10.1021/acs.orglett.4c03363
Org. Lett. 2024, 26, 8904–8909

generally relies on toxic and corrosive reagents,[7] we hypothesized that *N*-acyl imidazoliums might possess sufficient reactivity to engage carbon-centered nucleophiles. Considering the huge range of potential carbon-centered nucleophiles, Mayr's nucleophilicity scale helped define a meaningful starting point for these investigations.[8] Even though the *E* value for an *N*-acyl imidazolium ion has not been determined, we considered the *N*-values of anilines **3** and **4** as well as acyl hydrazide **5** known to react with carboxylic acids **1** at room temperature in the presence of TCFH–NMI (Figure 1).[9] Since pyrroles **6a–c** have *N* values approaching this range, the Mayr nucleophilicity scale suggests these could be competent nucleophiles for the *N*-acyl imidazolium ion.[10]

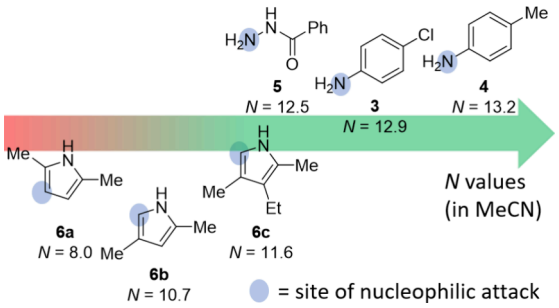
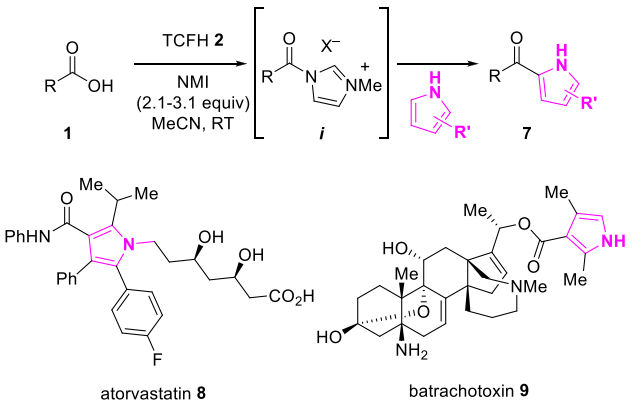


Figure 1. Comparison of known *N*-values of TCFH–NMI substrates **3–5** with those of pyrroles **6a–c**.

Focusing on pyrroles as nucleophiles provides access to a common motif in pharmaceutical compounds, illustrated by the tetrasubstituted pyrrole core of atorvastatin **8**, as well as the natural product batrachotoxin **9** (Scheme 2).[11] In this paper

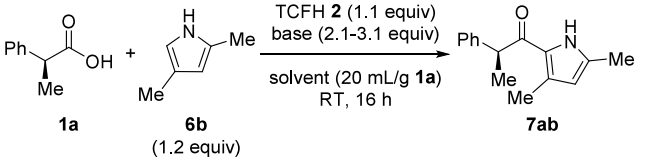
Scheme 2. Ketone Formation with TCFH–NMI



we describe the investigation of ketone formation with TCFH–NMI and highly nucleophilic pyrroles, guided and understood by consideration of Mayr's nucleophilicity parameters.

For the initial optimization, the substrate pair was chosen as (*S*)-2-phenylpropionic acid **1a**, which would allow us to assess reactivity as well as the integrity of the labile α-stereogenic center, and 2,4-dimethylpyrrole **6b**, for which the *N* value of 10.7 in acetonitrile (MeCN) is known.[10] Starting from established conditions in MeCN using 3.1 equiv of NMI as base gave good assay yield (AY) and low enantiopurity of the desired 5-acyl pyrrole **7ab** (Table 1).[12] Adjustment of the NMI stoichiometry to 2.1 equiv allowed for formation of the desired

Table 1. Optimization of Synthesis of 7ab with TCFH–NMI



entry	solvent	base (equiv)	CONV (%)[a]	AY (%)[b]	ee (%)[c]
1	MeCN	NMI (3.1)	84	73	20.5
2	MeCN	NMI (2.1)	76	61	98.6
3[d]	MeCN	NMI (2.1)	80	65	92.7
4	DCM	NMI (2.1)	89	73	97.4
5	THF	NMI (2.1)	75	62	64.6
6	DMF	NMI (2.1)	63	40	96.5
7	MeCN	NMM (2.1)	100	34	63.4
8	MeCN	NMM (2.0), DMAP (0.1)	35	9	ND
9	MeCN	DIPEA (2.1)	100	4	ND
10	MeCN	DIPEA (2.0), DMAP (0.1)	32	8	ND
11	MeCN	pyr (2.1)	0	0	ND
12	MeCN	DABCO (2.1)	45	7	ND
13	MeCN	DBU (2.1)	0	0	ND

[a]Conversion based on LC-UV area counts (AC) by CONV = 100 × (AC(**7ab**)/(AC(**1a**) + AC(**7ab**)), for example. Conversion values were not adjusted for response factor. [b]Assay yield (AY, %) was determined by LC-UV analysis of the reaction mixture; see Supporting Information page S2 for the detailed procedure. [c]Enantiomeric excess (ee) determined on crude reaction mixtures by LC-UV analysis. [d]Reaction at 40 °C.

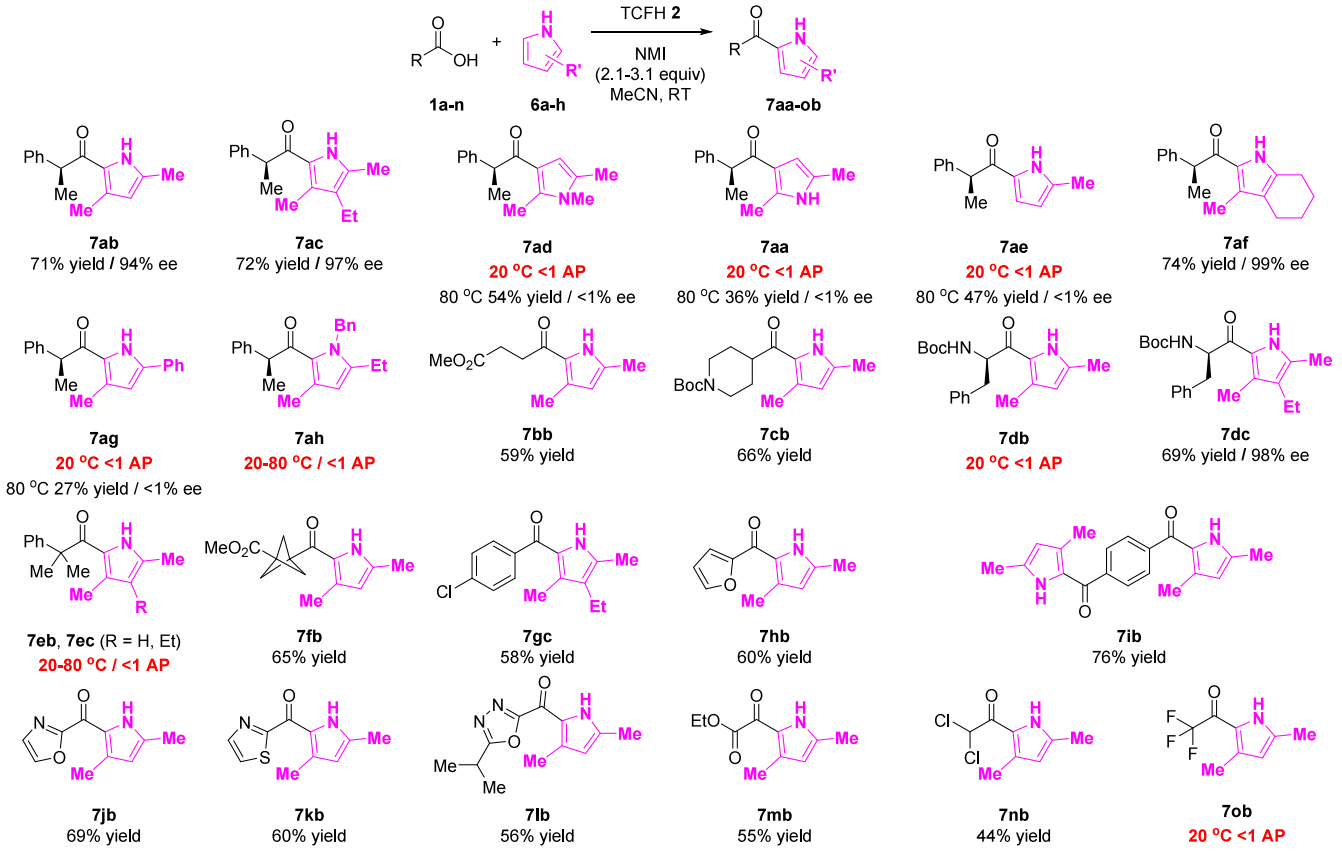
product in similar yield but no loss in enantiopurity (entries 1 and 2), consistent with a mechanism proceeding through an *N*-acylimidazolium ion ***i*** that requires 2 equiv of base as shown in Scheme 1. Warming the reaction to 40 °C led to a minor increase in conversion and yield but also induced epimerization (entry 3). Further screening of solvents demonstrated the reaction could proceed in other common solvents, but MeCN was preferred for its good yield, enantiopurity, environmental impact, and benefits for product isolation by addition of water (entries 4–6). An investigation of alternative bases emphasized the unique properties of NMI. Non-Lewis basic amines like *N*-methylmorpholine (NMM) and *N*,*N*-diisopropylethylamine (DIPEA) led to the formation of the unreactive anhydride rather than the desired ketone **7ab**, even in the presence of DMAP as a nucleophilic amine catalyst (entries 7–10). Other amines which combine Brønsted and Lewis basicity gave inferior results compared to NMI (entries 11–13).

Although TCFH is a unique amide bond-forming agent in terms of its simplicity and safety,[13] we wondered if other amide bond-forming agents exhibited similar reactivity. An examination of the reactivity of **1a** and **6b** in MeCN and NMI as base with other common amide bond-forming agents (CDI, EDAC, HATU, and T3P) revealed that only T3P could give good yield and enantiopurity of ketone **7ab** (72% AY, 95.5% ee).[14]

Starting from the high-yielding and mild conditions with TCFH–NMI, we examined the scope of the reaction with respect to the carboxylic acid as well as the pyrrole, guided by the *N* values measured by Mayr and co-workers (Scheme 3). Use of trisubstituted pyrrole **6c**, with an *N* value of 11.6, gave a comparable yield and minimal epimerization of the α-stereogenic center. Monitoring the rate of reaction of *N*-acyl imidazolium ion ***ii*** derived from **1a** with **6b** versus **6c** showed a significant increase in the reaction rate (k_{rel}(**6c**/**6b**) = 7),

https://doi.org/10.1021/acs.orglett.4c03363
Org. Lett. 2024, 26, 8904–8909

Scheme 3. Pyrroloketone Synthesis with TCFH–NMI



consistent with its higher *N* value (Figure 2). Examining the less-nucleophilic 1,2,5-trimethylpyrrole **6d** (N = 8.6), 2,5-dimethylpyrrole **6a** (N = 8.0), and 2-methylpyrrole **6e** revealed that less than 1 area percent (AP) of product was observed by LC-MS even after 72 h at room temperature. Heating to 80 °C in MeCN gave partial conversion after 16 h, with moderate yields of ketones **7ad**, **7aa**, and **7ae** with racemization. Further examination of pyrroles yielded mixed results, suggesting that these highly nucleophilic heteroaromatic species approach the reactivity limit of the *N*-acyl imidazolium ion. Tetrahydroindole **6f** gave good yield, whereas 2-phenyl-4-methylpyrrole **6g** as well as 1,2,4-substituted pyrrole **6h** showed only a trace amount of product after extended reaction times at room temperature. Heating to 80 °C led to the formation of ketone **7ag**, but **6h** remained unreactive.

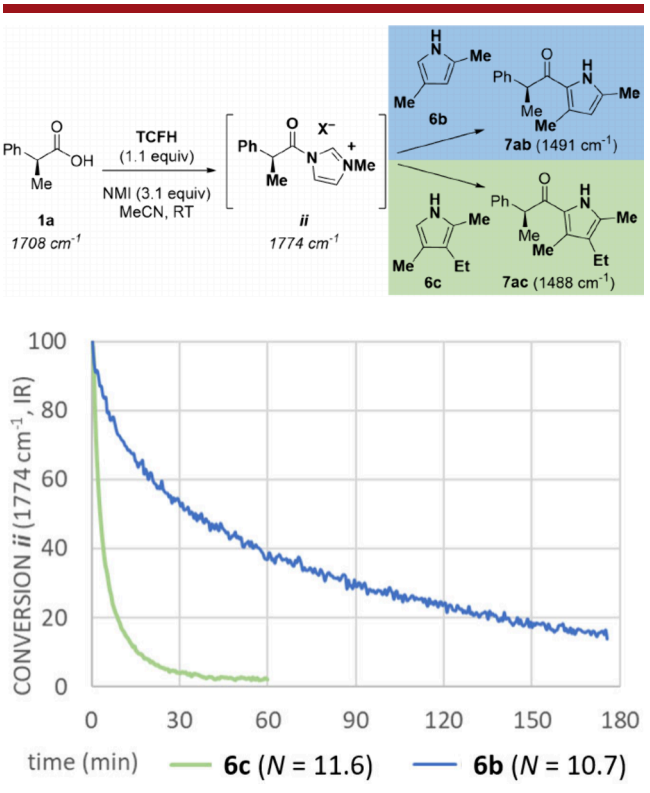


Figure 2. Kinetic profiles of the reactions of **6b** and **6c**.

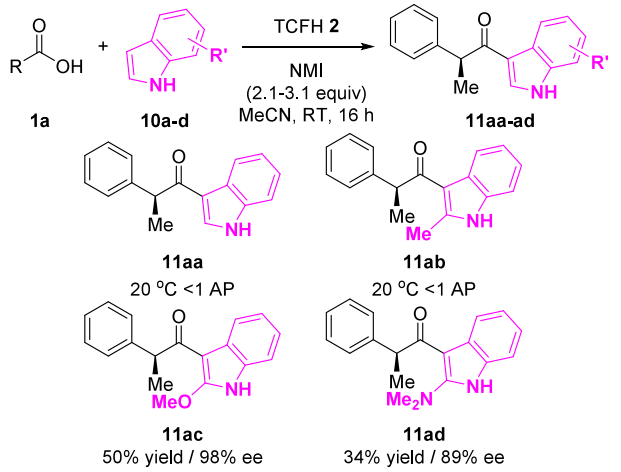
Further exploration of carboxylic acids showed that moderate to high yields could be obtained, generally with facile isolation of ketone product by addition of water and filtration. In general, chiral substrates can be run with 2.1 equiv of NMI while achiral substrates are run with 3.1 equiv. Primary carboxylic acid **1b** and secondary carboxylic acid **1c** afforded products **7bb** and **7cb** in good yield. Examination of the reaction of **6b** with Boc-protected amino acid **1d** gave less than 1 AP of **7db** after 72 h at room temperature, but the reaction with the more nucleophilic pyrrole **6c** provided a good yield and enantiopurity of product **7dc**. Tertiary carboxylic acid **1e** proved completely unreactive with pyrrole **6b** or the more reactive **6c**, but the conformationally restricted tertiary [1.1.1]bicyclopentane carboxylic acid **1f** gave a good yield of ketone **7fb**. A broad range of aromatic carboxylic acids **1g–1l**, notably heterocyclic carboxylic acids containing furan, oxazole, thiazole, and oxadiazole substituents, demonstrated good yields in reaction with **6b** and **6c**.[15] Terephthalic acid **6i**

https://doi.org/10.1021/acs.orglett.4c03363
Org. Lett. 2024, 26, 8904–8909

underwent a double substitution to give the bis-pyrrole product **7ib** in a good yield. The reactions of highly acidic species like oxalate ester **1m** (pK_a = 1.7 (H_2O))[16] and dichloroacetic acid **1n** (pK_a = 1.3 (H_2O))[17] underwent reaction with pyrrole **6b**, while more acidic carboxylic acids like trifluoroacetic acid (pK_a = 0.2 (H_2O))[18] did not provide the desired ketone product **7ob**.

Indoles were also investigated as potential nucleophiles. Indole **10a** itself (N = 5.6) is far less nucleophilic than the pyrroles examined in this study and showed no reactivity at room temperature.[19] 2-Methylindole **10b** (N = 6.9) was also unreactive, but 2-methoxy (**10c**) and 2-dimethylamino (**10d**) indole were reactive and led to moderate yields of ketone products **11ac** and **11ad**, consistent with the stronger electron-donating capacity of these heteroatomic groups (Scheme 4).

Scheme 4. Indoloketone Synthesis with TCFH−NMI



Ketone **11ac** was formed with a high level of enantiopurity, while ketone **11ad** showed some epimerization. Other constitutional isomers of methoxyindole were examined but proved unreactive, likely due to their low nucleophilicity (N = 5.4−6.2) compared to 2-methoxyindole.

To provide additional insight into the reaction scope with respect to the pyrrole nucleophile, we sought to expand on experimentally determined N values by seeking a computational correlation with the calculated methyl cation affinity (MCA) of these electron-rich aromatics.[20] Using experimental N values measured in MeCN, an excellent correlation was obtained at the B3LYP/6-311G++(3df,2pd) level of theory (Figure 3).[21] This allowed for a prediction of the N values for some substrates from the survey of the reaction scope and a good correlation with the reaction temperature required for reactivity (Table 2). The reactive tetrahydroindole **6f** was found to have an N value of 10.6, consistent with its high reactivity at room temperature. Computational predictions for 2-phenyl-4-methylpyrrole **6g** (N = 9.1) and 2-methylpyrrole **6e** (N = 8.9), which were unreactive at room temperature but demonstrated reactivity at 80 °C, appeared reasonable considering the similar reactivity of 1,2,5-trimethylpyrrole **6d** (N = 8.6) and 2,5-dimethylpyrrole **6a** (N = 8.0). 1,2,4-Substituted pyrrole **6h** was predicted to have an N value of 10.3, which seems at odds with its negligible reactivity at room temperature or 80 °C. However, considering the increased steric demands of reaction at the 5-position in **6h** highlights how caution should be used when applying these nucleophilicity and electrophilicity parameters to substrates with significant variation in steric demands.[22] In regard to the indole substrates, 2-methoxyindole **10c** was predicted to have an N of 9.8 and 2-dimethylaminoindole **10d** an N of 12.1, helping rationalize their enhanced reactivity compared to other indoles (N < 7).

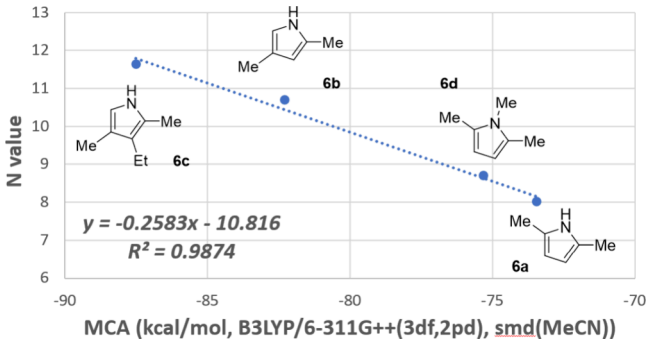


Figure 3. Plot of calculated MCAs and experimental N values.

Table 2. Relation of the N Value and Reaction Temperature

Substrate	N (calc/exp)[1]	reaction temp (°C)
10d	12.1 (calc)	20
6c	11.6 (exp)[3]	20
6b	10.7 (exp)[3]	20
6f	10.6 (calc)	20
6h	10.3 (calc)	NR[2]
10c	9.8 (calc)	20
6g	9.1 (calc)	80
6e	8.9 (calc)	80
6d	8.6 (exp)[3]	80
6a	8.0 (exp)[3]	80
10b	6.9 (exp)[4]	NR[2]
10a	5.6 (exp)[4]	NR[2]

[a]exp = experimental, calc = DFT prediction. [b]NR = no reaction at 20 or 80 °C. [c]See ref 10. [d]See ref 19.

In conclusion, this paper continues to expand the scope of TCFH−NMI as an activating agent for carboxylic acids to the preparation of ketones with carbon-centered nucleophiles. To identify a reasonable starting point for these investigations, the Mayr nucleophilicity scales were consulted using the N values of known, reactive nitrogen nucleophiles from reactions promoted by TCFH−NMI. This led to the selection of highly nucleophilic heterocycles such as pyrroles as substrates. The resulting scope of ketone formation with TCFH−NMI can be clearly understood in the context of Mayr's nucleophilicity scale, recognizing that $N \geq 10$ is required for room temperature reactivity with an N-acyl imidazolium ion intermediate. The success of this model in a complex system across a range of nucleophiles, even when the E value of the electrophile is not known, emphasizes the predictive power of Mayr's reactivity scale in modern methodology development.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

https://doi.org/10.1021/acs.orglett.4c03363
Org. Lett. 2024, 26, 8904−8909

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03363.

Additional screening data, detailed experimental procedures, characterization, DFT coordinates, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **6h**, **7aa**–**7nb**, **11ac**, and **11ad** (ZIP)

AUTHOR INFORMATION

Corresponding Authors

Gregory L. Beutner − *Chemical Process Development, Bristol Myers Squibb Company, New Brunswick, New Jersey 08903, United States*; orcid.org/0000-0001-8779-1404; Email: gregory.beutner@bms.com

David A. Vosburg − *Department of Chemistry, Harvey Mudd College, Claremont, California 91711, United States*; Email: vosburg@g.hmc.edu

Authors

Johnson H. Ho − *Department of Chemistry, Harvey Mudd College, Claremont, California 91711, United States*

Grant H. Miller − *Department of Chemistry, Harvey Mudd College, Claremont, California 91711, United States*

Kasey K. Chung − *Department of Chemistry, Harvey Mudd College, Claremont, California 91711, United States*

Sydney D. Neibert − *Department of Chemistry, Harvey Mudd College, Claremont, California 91711, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.4c03363

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Dr. Sloan Ayers (BMS) for assistance with NMR spectroscopy, Drs. Ethan Van Arnam and Anna Wenzel (Pitzer and Scripps Colleges) for assistance with HRMS, and Drs. Rodney Parsons and Antonio Ramirez (BMS) for their assistance in the preparation of this manuscript. This work was supported by the Harvey Mudd College Department of Chemistry, the Rasmussen Summer Research Fund (J.H.H. and K.K.C.), an Organic Syntheses Summer Research Grant (G.H.M.), and NSF-MRI grants CHE-0922481 (HMC, HPLC) and CHE-1725142 (HMC, NMR).

REFERENCES

(1) (a) Mayr, H.; Patz, M. Scales of Nucleophilicity and Electrophilicity: A System for Ordering Polar Organic and Organometallic Reactions. *Angewandte Chemie International Edition in English* **1994**, *33*, 938−957. (b) Mayr, H.; Ofial, A. R. Kinetics of electrophile-nucleophile combinations: A general approach to polar organic reactivity. *Pure Appl. Chem.* **2005**, *77*, 1807−1821.

(2) Mayr, H.; Ofial, A. R. Do general nucleophilicity scales exist? *J. Phys. Org. Chem.* **2008**, *21*, 584−595.

(3) Ofial, A. R. Mayr's Database Of Reactivity Parameters. https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/ (accessed May 10, 2024).

(4) (a) Chamorro, E.; Duque-Noreña, M.; Pérez, P. Further relationships between theoretical and experimental models of electrophilicity and nucleophilicity. *Journal of Molecular Structure: THEOCHEM* **2009**, *901*, 145−152. (b) Wang, C.; Fu, Y.; Guo, Q.-X.; Liu, L. First-Principles Prediction of Nucleophilicity Parameters for π Nucleophiles: Implications for Mechanistic Origin of Mayr's Equation. *Chemistry − A European Journal* **2010**, *16*, 2586−2598. (c) Zhuo, L.-G.; Liao, W.; Yu, Z.-X. A Frontier Molecular Orbital Theory Approach to Understanding the Mayr Equation and to Quantifying Nucleophilicity and Electrophilicity by Using HOMO and LUMO Energies. *Asian Journal of Organic Chemistry* **2012**, *1*, 336−345.

(5) (a) Beutner, G. L.; Young, I. S.; Davies, M. L.; Hickey, M. R.; Park, H.; Stevens, J. M.; Ye, Q. TCFH−NMI: Direct Access to N-Acyl Imidazoliums for Challenging Amide Bond Formations. *Org. Lett.* **2018**, *20*, 4218−4222. (b) Baldwin, O. W. M.; Conrad-Marut, L. H.; Beutner, G. L.; Vosburg, D. A. Facile Amide Bond Formation with TCFH−NMI in an Organic Laboratory Course. *J. Chem. Educ.* **2022**, *99*, 3747−3751. (c) Luis, N. R.; Chung, K. K.; Hickey, M. R.; Lin, Z.; Beutner, G. L.; Vosburg, D. A. Beyond Amide Bond Formation: TCFH as a Reagent for Esterification. *Org. Lett.* **2024**, *26*, 2745−2750.

(6) (a) Wang, H.; Gong, C.; Zhang, C.; Zheng, X.; Hou, Q.; Zhou, Q.; Zhou, G.; Chen, Y. Ag(I)/CAAA-Amidphos Complex Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Acrylates for the Formal Synthesis of (+)-Ibophyllidine. *Synlett* **2021**, *32*, 1437−1446. (b) Goldfogel, M. J.; Jamison, C. R.; Savage, S. A.; Haley, M. W.; Mukherjee, S.; Sfouggatakis, C.; Gujjar, M.; Mohan, J.; Rakshit, S.; Vaidyanathan, R. Development of Two Synthetic Approaches to an APJ Receptor Agonist Containing a Tetra-ortho-Substituted Biaryl Pyridone. *Org. Process Res. Dev.* **2022**, *26*, 624−634. (c) You, Q.; Guo, X.; Feng, Q.; Wang, Y.; Jiang, R.; Jiang, Z.; Jiang, Z.; Xu, X. Preparation of substituted pyridine derivative as ALKBH5 inhibitors for treatment of ALKBH5 dysfunction related diseases. CN115806522A, 2023.

(7) (a) Achmatowicz, M. M.; Thiel, O. R.; Colyer, J. T.; Hu, J.; Elipe, M. V. S.; Tomaskevitch, J.; Tedrow, J. S.; Larsen, R. D. Hydrolysis of Phosphoryl Trichloride (POCl3): Characterization, in Situ Detection, and Safe Quenching of Energetic Metastable Intermediates. *Org. Process Res. Dev.* **2010**, *14*, 1490−1500. (b) Treitler, D. S.; Soumeillant, M. C.; Simmons, E. M.; Lin, D.; Inankur, B.; Rogers, A. J.; Dummeldinger, M.; Kolotuchin, S.; Chan, C.; Li, J.; Freitag, A.; Lora Gonzalez, F.; Smith, M. J.; Sfouggatakis, C.; Wang, J.; Benkovics, T.; Deerberg, J.; Simpson, J. H.; Chen, K.; Tymonko, S. Development of a Commercial Process for Deucravacitinib, a Deuterated API for TYK2 Inhibition. *Org. Process Res. Dev.* **2022**, *26*, 1202−1222.

(8) Mayr, H.; Kempf, B.; Ofial, A. R. π-Nucleophilicity in Carbon−Carbon Bond-Forming Reactions. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(9) (a) Brotzel, F.; Chu, Y. C.; Mayr, H. Nucleophilicities of Primary and Secondary Amines in Water. *Journal of Organic Chemistry* **2007**, *72*, 3679−3688. (b) Baidya, M.; Brotzel, F.; Mayr, H. Nucleophilicities and Lewis basicities of imidazoles, benzimidazoles, and benzotriazoles. *Organic & Biomolecular Chemistry* **2010**, *8*, 1929−1935. (c) Nigst, T. A.; Antipova, A.; Mayr, H. Nucleophilic Reactivities of Hydrazines and Amines: The Futile Search for the α-Effect in Hydrazine Reactivities. *Journal of Organic Chemistry* **2012**, *77*, 8142−8155.

(10) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Pyrroles. *Eur. J. Org. Chem.* **2008**, *2008*, 2369−2374.

(11) (a) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. Pyrrole: a resourceful small molecule in key medicinal heteroaromatics. *RSC Adv.* **2015**, *5*, 15233−15266. (b) Jeelan Basha, N.; Basavarajaiah, S. M.; Shyamsunder, K. Therapeutic potential of pyrrole and pyrrolidine analogs: an update. *Molecular Diversity* **2022**, *26*, 2915−2937.

(12) Wang, Q.-Y.; Liu, T.-F.; Chu, L.-F.; Yao, Y.; Lu, C.-D. Chiral spiro phosphoric acid-catalysed enantioselective reaction of ketenes with N−H pyrroles. *Chem. Commun.* **2021**, *57*, 11992−11995.

(13) Graham, J. C.; Trejo-Martin, A.; Chilton, M. L.; Kostal, J.; Bercu, J.; Beutner, G. L.; Bruen, U. S.; Dolan, D. G.; Gomez, S.; Hillegass, J.; Nicolette, J.; Schmitz, M. An Evaluation of the

Occupational Health Hazards of Peptide Couplers. *Chem. Res. Toxicol.* **2022**, *35*, 1011−1022.
(14) See the Supporting Information page S3 for full details.
(15) Guo, Z.; Wei, X.; Hua, Y.; Chao, J.; Liu, D. Synthesis of 2-benzoylpyrrole derivatives via C−H functionalization adjacent to nitrogen of pyrrole. *Tetrahedron Lett.* **2015**, *56*, 3919−3922.
(16) Johnson, G. L.; Angelici, R. J. Metal-ion catalysis of ethyl oxalate hydrolysis. *J. Am. Chem. Soc.* **1971**, *93*, 1106−1110.
(17) McManus, J. B.; Griffin, J. D.; White, A. R.; Nicewicz, D. A. Homobenzylic Oxygenation Enabled by Dual Organic Photoredox and Cobalt Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 10325−10330.
(18) Reinhardt, L. A.; Sacksteder, K. A.; Cleland, W. W. Enthalpic Studies of Complex Formation between Carboxylic Acids and 1-Alkylimidazoles. *J. Am. Chem. Soc.* **1998**, *120*, 13366−13369.
(19) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Indoles. *Journal of Organic Chemistry* **2006**, *71*, 9088−9095.
(20) (a) Wei, Y.; Singer, T.; Mayr, H.; Sastry, G. N.; Zipse, H. Assessment of theoretical methods for the calculation of methyl cation affinities. *J. Comput. Chem.* **2008**, *29*, 291−297. (b) Hensinger, M. J.; Eitzinger, A.; Trapp, O.; Ofial, A. R. Nucleophilicity of 4-(Alkylthio)-3-imidazoline Derived Enamines. *Chemistry − A European Journal* **2024**, *30*, No. e202302764.
(21) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, rev. C.01; Gaussian, Inc.: Wallingford, CT, 2016.
(22) Follet, E.; Mayer, P.; Mayr, H. Lewis Acidities of Indol-3-ylmethylium Ions and Intrinsic Barriers of Their Reactions with Phosphines and Pyridines. *Eur. J. Org. Chem.* **2016**, *2016*, 4050−4058.

https://doi.org/10.1021/acs.orglett.4c03363
Org. Lett. 2024, 26, 8904−8909