Title

Mild Sustainable Amide Alkylation Protocol Enables a Broad Orthogonal Scope

Journal

The Journal of Organic Chemistry, 87(18)

ISSN

0022-3263

Authors

Hibbard, Jason P

Yam, Jessalyn G

Alsalek, Eyad B

et al.

Publication Date

2022-09-16

DOI

10.1021/acs.joc.2c01028

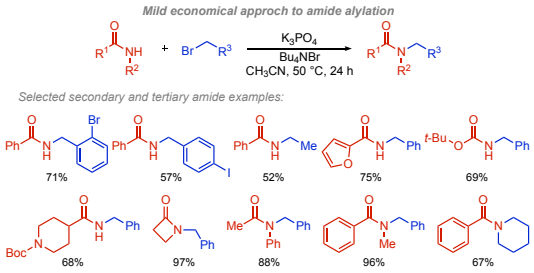
Mild Sustainable Amide Alkylation Protocol Enables a Broad Orthogonal Scope

Jason P. Hibbard, Jessalyn G. Yam, Eyad B. Alsalek, Ana Bahamonde*

Chemistry, University of California, Riverside. 501 Big Springs Rd., Riverside, CA 92521, United States.

Supporting Information Placeholder

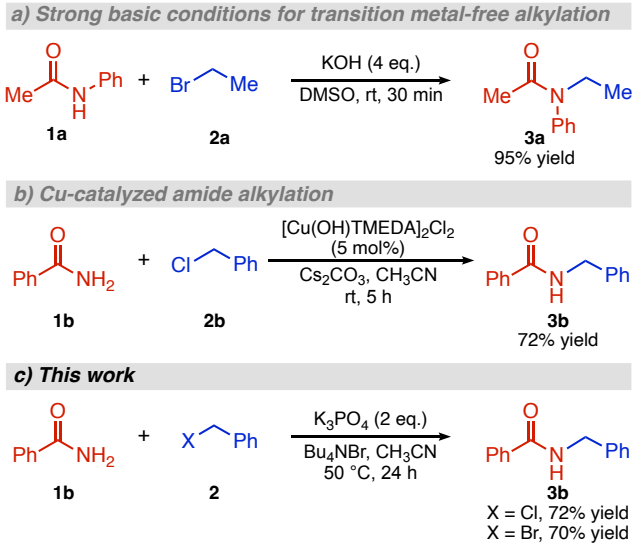
ABSTRACT Herein, the development of a mild sustainable protocol to couple primary alkyl chlorides and bromides with amides is described. In contrast to current methodologies, our system does not require the use of strongly basic conditions, high temperatures, or the addition of an organometallic catalyst, thereby enabling access to a remarkably orthogonal scope. K_3PO_4 is used to facilitate the formation of secondary and tertiary amides, which are ubiquitous scaffolds in bioactive molecules and natural products. Alkylated amide products are obtained in good to excellent yields, with no substantial limitations observed based on the steric and electronic properties of either coupling partner.



INTRODUCTION

Amides are not only versatile building blocks in the synthesis of amines and carbonyl compounds but are also a prevalent motif in polymers, natural products, and commercial drugs.[1] Indeed, the condensation of amines with acyl electrophiles to yield amides accounts for ~16% of the reactions performed in the pharmaceutical industry.[2] Typically acyl chlorides, or carboxylic acids in conjunction with a coupling agent to facilitate dehydration, are employed in these transformations.[3] Although a large array of coupling agents have been reported, the optimal conditions still remain case-specific and it is difficult to predict what the best conditions will be without carrying out extensive optimization studies.[1c] Hence, establishing general protocols that enable access to a wide scope of amides would represent a synthetic advance.

An alternative approach to amide synthesis is the derivatization of preexisting amides. Among the strategies developed in this area, amide arylation reactions have been extensively studied, with Pd- and Cu-catalyzed processes predominating in the literature.[4] In contrast, amide alkylation has proven to be more elusive and is often only achievable via quantitative amide deprotonation using an excess of a strong base in highly polar solvents. Subsequently, the amidate nucleophile adds to alkyl halides via S_N1- or S_N2-type substitution mechanisms (Scheme 1a).[5] Often, these reported strategy rely of the use of microwave irradiation and phase transfer catalysts to facilitate the amide deprotonation and subsequent nucleophilic attack.[5e, 5f] To avoid the use of high pH solutions and broaden the reaction scope, organometallic complexes have been utilized.[6] These procedures enable the use of milder bases like carbonates or phosphates. However, most metal-catalyzed transformations still require high temperatures to proceed. Among those, the most closely related to the system described in this manuscript are the scarce examples describing the use of Cu catalysts to facilitate the coupling of alkyl halides to amides without requiring strongly basic conditions (Scheme 1b).[6a, 6c-e, 6h]



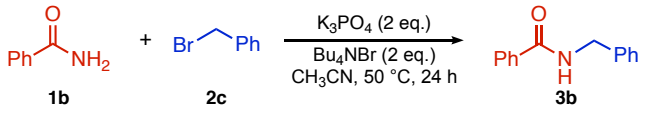
Scheme 1. Amide alkylation strategies using alkyl halides.

The reduced number of reports leveraging organometallic catalysts to forge new C–N bonds is a general trend that expands beyond amide functionalization, and can also be generally observed when surveying transition metal-mediated strategies for constructing C–C versus C–N bonds.[7] One of the main challenges hampering the development of these reactions is that nitrogen nucleophiles often act as strong ligands, such that reductive elimination tends to be rate-limiting, especially for $C(sp^3)$–N coupling. Additionally, metal-mediated amide functionalizations are highly sensitive to steric hindrance around the nitrogen, with limited examples reported for the functionalization of acyclic secondary amides.[6b, 6h, 6i] Thus, the development of alternative amide alkylation protocols for functionalizing both primary and secondary amides under mild conditions that are compatible with a broad array of functional groups would be highly desirable.

RESULTS AND DISCUSSION

Herein, an unexpected strategy for coupling alkyl halides with primary and secondary amides will be described. This methodology does not require strongly basic conditions, high temperatures, or transition metal additives. Specifically, we have identified that mixtures of K_3PO_4 in acetonitrile, a medium in which the moderately basic salt is very poorly soluble, can facilitate this elusive transformation (Scheme 1c). This study showcases how this inexpensive procedure presents a robust and generalizable alternative to the current methodologies, affording a wide variety of secondary and tertiary amides in good to excellent yields.

Table 1. Effect of reaction parameters on K_3PO_4-mediated amide alkylation.



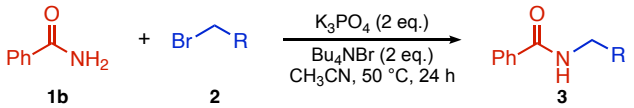
1b **2c** **3b**

Entry	Change from the standard conditions	Yield (%)[a]
1	**none**	**82 (70)**[b]
2	Na_3PO_4, instead of K_3PO_4	20
3	K_2HPO_4, instead of K_3PO_4	<5
4	K_2CO_3, instead of K_3PO_4	8
5	NaOAc, instead of K_3PO_4	<5
6	No Bu_4NBr	63
7	Room temperature	20
8	THF, instead of CH_3CN	60
9	DMSO, instead of CH_3CN	31
10	DMF, instead of CH_3CN	12
11	2 equivalents of H_2O added	79

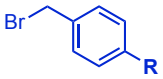
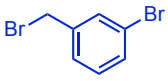
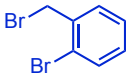
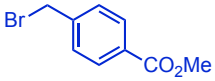
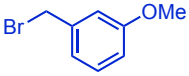
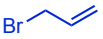
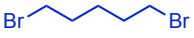
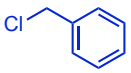
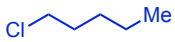
General conditions: reactions performed on a 0.3 mmol scale using 2 eq. of amide **1** and 1.5 mL of CH_3CN. [a] Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Yield of purified product (average of two experiments).

During the optimization campaign, the coupling of benzamide (**1b**) and benzyl bromide (**2c**) was selected as a model reaction (Table 1, see SI for further information). It was observed that optimal reactivity was achieved with the potassium phosphate tribasic salt when acetonitrile was used as the solvent in the presence of tetrabutylammonium bromide as a phase transfer catalyst. Several other mild inorganic bases afforded little to no observed reactivity, apart from a moderate 20% yield obtained using the sodium analogue of the tribasic phosphate salt (entries 2-5). In contrast with previously reported methodologies where the phase transfer agent pays a key role a zeroth order is observed with respect to this reaction component and the exclusion of tetrabutylammonium bromide resulted in a modest reduction in yield (entry 6).[5d-f] Conducting the reaction at room temperature led to a substantial yield decrease (from 70% to 20% yield, entry 7). Under the optimized conditions, other polar solvents like tetrahydrofuran (THF), dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) also facilitated the formation of the alkylated amide **3b**, albeit in lower yields (entries 8-10). The presence of water is tolerated, as a negligible yield reduction was observed upon the addition of 2 equivalents of water (entry 11).

Table 2. Primary alkyl halide electrophile scope for K_3PO_4-mediated amide alkylation.



1b **2** **3**

Entry	Electrophile (**2**)	Yield [a]
		
1	**R** = H	**3b**: 70%
2	Cl	**3c**: 63%
3	Br	**3d**: 53%
4	I	**3e**: 57%
5		**3f**: 59%
6		**3g**: 71%
7		**3h**: 50%
8		**3i**: 81%
9		**3j**: 67%
10		**3k**: 52%[b]
11		**3l**: 58%[b]
12		**3m**: 67%[b,c]
13		**3b**: 72%
14		**3l**: 52%[b]

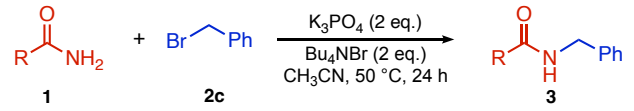
General conditions: reactions performed on a 0.3 mmol scale using 2 eq. of amide **1b** and 1.5 mL of CH_3CN. [a] Yield of purified product (average of two experiments). [b] 48 h reaction time. [c] Yield of cyclic tertiary amide as the double alkylation product. 3 equivalents of K_3PO_4 were used.

Intrigued by the simplicity of the reaction conditions, which do not require the addition of a transition metal and seem to rely on the sole action of K_3PO_4 (a base that has been used before in conjunction with organometallic catalysts to afford these same couplings),[6e] we initially focused on testing the reproducibility of the reaction. Multiple batches of K_3PO_4 from two different providers were tested and gave comparable results, as did using acetonitrile of varying grades. To discard the presence of a pervasive contaminant in our laboratory's reagents, the reaction was also reproduced in the laboratory of Professor Melchiorre at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain. Following the procedure detailed in the supporting information, alkylated amide **3b** was isolated in

66%, which is nearly identical to the 70% yield obtained in our laboratory (Scheme 1c).

With the optimized conditions in hand, we began exploring the reaction scope (Table 2). Motivated by the absence of an organometallic catalyst, functional groups that are susceptible to oxidative addition, and thus incompatible with most current methodologies, were tested. In this context, a series of benzyl bromides bearing aryl chlorides, bromides and iodides were found to be viable substrates for the reaction (entries 2-6). Of special interest is the tolerance of this methodology to aryl iodides and the excellent yield obtained for *ortho*-substituted benzyl bromides (entries 4 and 6, respectively). Other functional groups like a base-sensitive methyl ester or methoxy groups are also tolerated (entries 7 and 8). The use of allylic bromide was also successful, leading to the formation of the allylated amide in a moderate yield (entry 9).

Table 3. Primary amide scope for K_3PO_4-mediated amide alkylation.



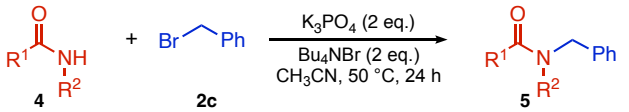
Entry	Amide (**1**)	Yield [a]
1	**R** = H	**3b**: 70%
2	Br	**3n**: 68%
3	I	**3o**: 57%
4	CF_3	**3p**: 73%
5	OMe	**3q**: 59%
6		**3r**: 63%
7		**3s**: 75%
8		**3t**: 74%
9		**3u**: 69%
10		**3v**: 58%[b]
11		**3w**: 58%[b]
12		**3x**: 68%[b]
13		**3y**: 59%[b]
14		**3z**: 66%
15		**3aa**: 69%

General conditions: reactions performed on a 0.3 mmol scale using 2 eq. of amide **1** and 1.5 mL of CH_3CN. [a] Yield of purified product (average of two experiments). [b] 48 h reaction time.

The scope expands beyond the use of conjugated bromides to include unactivated alkyl bromides (entries 10-12 and 14). The reduced reactivity of these electrophiles was overcome with longer reaction times to enable the corresponding alkylated amides to be generated in moderate to good yields. Notably, when reacting benzamide **1b** with 1,5-dibromopentane, initial alkylation occurred followed by intramolecular cyclization via a second *N*-alkylation to form the cyclized tertiary amide product in good yield (entry 12). The use of secondary alkyl bromides was not successful and resulted in only trace amounts of product. Finally, when benzyl chloride (**2b**) or 1-chloropentane were used as electrophiles, the desired products were isolated in comparable yield to that obtained with the corresponding bromides (c.f., entries 13 and 1 and entries 14 and 11).

The scope for *N*-alkylation of primary amides is presented in Table 3. Aromatic amides with both electron donating and electron withdrawing groups were tolerated, leading to the desired products in good to moderate yields (entries 1-5). Once again, aryl halides, including aryl iodides, were tolerated. Extended π-systems, heterocycles, and acrylamide displayed similar reactivity to that of benzamide (entries 6-8). Both cyclic and acyclic aliphatic amides were also amenable to the reaction (entries 9-14). We were pleased to find that there is no significant impact of the amide steric congestion (entries 13 and 14) on the reaction yield. Furthermore, comparable results were obtained when subjecting *tert*-butyl carbamate to the reaction conditions (entry 15), which upon acidic work-up allows access to the corresponding amine.

Table 4. Secondary amide scope for K_3PO_4-mediated amide alkylation.



Entry	Amide (**4**)	Yield [a]
1		**5a**: 78%
2		**5b**: 92%
3		**5c**: 97%
4		**5d**: 86%
5		**5e**: 74%
6		**5f**: 96%
7		**5g**: 88%

General conditions: reactions performed on a 0.3 mmol scale using 2 eq. of amide **4** and 1.5 mL of CH_3CN. [a] Yield of purified product (average of two experiments).

Perhaps the most remarkable result was obtained when testing the reactivity of less acidic and more hindered secondary amides, where the corresponding alkylated tertiary amides were isolated in exceptional yields (Table 4). Cyclic amides of various ring sizes, including an oxazolidinone and a β-lactam, reacted to form the benzylated product in excellent yields (entries 1-4). Additionally, this protocol was able to facilitate the previously elusive alkylation of acyclic secondary amides in high yields (entries 5-7). Similarly to the primary amide scope (Table 3), no substantial effect on the reaction yield was observed upon varying the electronic or steric environments around the amide.

The most intriguing aspect of the observed reactivity is the discrepancy between the acidity of the amides and the moderate basicity of the K_3PO_4 base (15.1 for acetamide versus 12.3 for HPO_4^{2-} in water).[8] Considering the marked solvent effect observed on reactivity (Table 1), we attempted to measure the pK_a of the conjugate acid of K_3PO_4 in acetonitrile. Unfortunately, the poor solubility of the

inorganic salt in acetonitrile, even in the presence of NBu_4Br, precluded the pK_a from being measured. Unable to obtain an experimental value, ΔG for the reaction between benzamide **1b** and K_3PO_4 in acetonitrile was calculated to be +4.0 kcal/mol at the M06-D3/6-311++G(d,p) // B3LYP-D3BJ/6-311++G(d,p) level of theory with implicit SMD solvation (see SI).[9] Similarly to the acid-base equilibrium measurements in water, these calculations suggest that the deprotonation equilibrium in acetonitrile is also unfavorable.

In light of this data, it is proposed that the moderately basic K_3PO_4 likely facilitates amide deprotonation to at least a sufficient extent to enable a subsequent nucleophilic attack into the alkyl halide to forge the new C–N bond. It is believed that a key factor for the large functional group compatibility is the low concentration in solution of the reactive amidate. The low amidate concentration is the consequence of both the aforementioned pK_a discrepancy and the poor solubility of K_3PO_4 in acetonitrile. The reproducibility of the reaction through multiple batches, providers, and laboratories suggests that the involvement of a pervasive Lewis acidic impurity in K_3PO_4, which could assist in facilitating amide deprotonation, is unlikely. However, this possibility cannot be discarded.

CONCLUSIONS

In summary, the methodology described in this paper allows the alkylation of a wide breadth of both primary and secondary amides under mild conditions without requiring the addition of a transition metal catalyst. The scope of this transformation presents an orthogonal functional group tolerance to those of previously reported strategies, highlighted by the compatibility of aryl halides, including aryl iodides, and the excellent yields obtained for the alkylation of hindered acyclic secondary amides. It is believed that the robustness of this protocol, which does not require the use of dry conditions or inert atmospheres, the remarkable scope, and the use of economical reagents will collectively make this strategy an attractive approach to late-stage amide functionalization for the synthetic community.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, characterization data, copies of NMR spectra of all compounds, and computational data (PDF)

AUTHOR INFORMATION

Corresponding Author

* ana.bahamonde@ucr.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the University of California, Riverside. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1548562. We thank Prof. Paolo Melchiorre and Davide Spinnato for their help studying the reproducibility of the system.

REFERENCES

1. (a) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M., Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discov.* **2018,** *17*, 709-727; (b) Bray, B. L., Large-scale manufacture of peptide therapeutics by chemical synthesis. *Nat. Rev. Drug Discov.* **2003,** *2*, 587-593; (c) Dunetz, J. R.; Magano, J.; Weisenburger, G. A., Large-scale applications of amide coupling reagents for the synthesis of pharmaceuticals. *Org. Process Res. Dev.* **2016,** *20*, 140-177; (d) Greenberg, A.; Breneman, C. M.; Liebman, J. F., *The amide linkage: Structural significance in chemistry, biochemistry, and materials science*. John Wiley & Sons: 2002.

2. (a) Roughley, S. D.; Jordan, A. M., The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **2011,** *54*, 3451-3479; (b) Brown, D. G.; Bostrom, J., Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective. *J. Med. Chem.* **2016,** *59*, 4443-4458.

3. (a) Valeur, E.; Bradley, M., Amide bond formation: beyond the myth of coupling reagents. *Chem. Soc. Rev.* **2009,** *38*, 606-631; (b) Montalbetti, C. A.; Falque, V., Amide bond formation and peptide coupling. *Tetrahedron* **2005,** *61*, 10827-10852.

4. (a) Dorel, R.; Grugel, C. P.; Haydl, A. M., The Buchwald–Hartwig amination after 25 years. *Angew. Chem. Int. Ed.* **2019,** *58*, 17118-17129; (b) Klapars, A.; Huang, X.; Buchwald, S. L., A general and efficient copper catalyst for the amidation of aryl halides. *J. Am. Chem. Soc.* **2002,** *124*, 7421-7428; (c) Surry, D. S.; Buchwald, S. L., Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chem. Sci.* **2011,** *2*, 27-50.

5. (a) Beckwith, A., Synthesis of amides. *Amides (1970)* **1970**, 73-185; (b) Fones, W. S., The use of sodium hydride in the alkylation of N-substituted amides. *J. Org. Chem.* **1949,** *14*, 1099-1102; (c) Johnstone, R. A.; Rose, M. E., A rapid, simple, and mild procedure for alkylation of phenols, alcohols, amides and acids. *Tetrahedron* **1979,** *35*, 2169-2173; (d) Ayyangar, N.; Choudhary, A.; Kalkote, U.; Natu, A., A Simple and Economical Method for the Alkylation of Benzanilides1. *Synthetic Communications* **1988,** *18*, 2011-2016; (e) Bogdal, D., Fast solvent-free alkylation of amides and lactams under microwave irradiation. *Molecules* **1999,** *4*, 333-337; (f) Greiner, I.; Sypaseuth, F. D.; Grun, A.; Karsai, E.; Keglevich, G., The role of phase transfer catalysis in the microwave-assisted N-benzylation of amides, imides and N-heterocycles. *Letters in Organic Chemistry* **2009,** *6*, 529-534.

6. (a) Chen, C.; Peters, J. C.; Fu, G. C., Photoinduced copper-catalysed asymmetric amidation via ligand cooperativity. *Nature* **2021,** *596*, 250-256; (b) Dai, X.; Shi, F., N-Alkyl amide synthesis via N-alkylation of amides with alcohols. *Org. Biomol. Chem.* **2019,** *17*, 2044-2054; (c) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C., Photoinduced, copper-catalyzed alkylation of amides with unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **2014,** *136*, 2162-2167; (d) Fung, A. K.; Yu, L.-J.; Sherburn, M. S.; Coote, M. L., Atom Transfer Radical Polymerization-Inspired Room Temperature (sp3) C–N Coupling. *J. Org. Chem.* **2021,** *86*, 9723-9732; (e) Kumaraswamy, G.; Pitchaiah, A.; Ramakrishna, G.; Ramakrishna, D.; Sadaiah, K., Di-μ-hydroxy-bis (N, N, N′, N′-tetramethylenediamine)-copper (II) chloride [Cu (OH)· TMEDA] 2Cl2: an efficient, practical catalyst for benzylation and allylation of amides. *Tetrahedron Lett.* **2006,** *47*, 2013-2015; (f) Das, J.; Banerjee, D., Nickel-Catalyzed Phosphine Free Direct N-Alkylation of Amides with Alcohols. *J. Org. Chem.* **2018,** *83*, 3378-3384; (g) Wan, J.-P.; Jing, Y., Recent advances in copper-catalyzed C–H bond amidation. *Beilstein J. Org. Chem.* **2015,** *11*, 2209-2222; (h) Zheng, Y.-W.; Narobe, R.; Donabauer, K.; Yakubov, S.; König, B., Copper(II)-Photocatalyzed N–H Alkylation with Alkanes. *ACS Catal.* **2020,** *10*, 8582-8589; (i) Rovira, M.; Soler, M.; Güell, I.; Wang, M.-Z.; Gómez, L.; Ribas, X., Orthogonal Discrimination among Functional Groups in Ullmann-Type C–O and C–N Couplings. *J. Org. Chem.* **2016,** *81*, 7315-7325.

7. (a) Diederich, F.; Stang, P. J., *Metal-catalyzed cross-coupling reactions*. John Wiley & Sons: 2008; (b) Hartwig, J. F., Carbon– heteroatom bond-forming reductive eliminations of amines, ethers, and sulfides. *Acc. Chem. Res.* **1998,** *31*, 852-860; (c) Ricci, A., *Modern amination methods*. John Wiley & Sons: 2008.

8. Ripin, D.; Evans, D., pKa's of Inorganic and Oxo-Acids. *The Evans* **2005**.

9. (a) Becke, A. D.; Johnson, E. R., A density-functional model of the dispersion interaction. *J. Chem. Phys.* **2005,** *123*, 154101; (b) Frisch, M.; Trucks, G.; Schlegel, H.; Scuseria, G.; Robb, M.; Cheeseman, J.; Scalmani, G.; Barone, V.; Petersson, G.; Nakatsuji, H., Gaussian 16. Gaussian, Inc. Wallingford, CT: 2016; (c) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010,** *132*, 154104; (d) Grimme, S.; Ehrlich, S.; Goerigk, L., Effect of the damping function in dispersion corrected

density functional theory. *J. Comput. Chem.* **2011,** *32*, 1456-1465; (e) Johnson, E. R.; Becke, A. D., A post-Hartree-Fock model of intermolecular interactions: Inclusion of higher-order corrections. *J. Chem. Phys.* **2006,** *124*, 174104; (f) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009,** *113*, 6378-6396; (g) Towns, J.; Cockerill, T.; Dahan, M.; Foster, I.; Gaither, K.; Grimshaw, A.; Hazlewood, V.; Lathrop, S.; Lifka, D.; Peterson, G. D., XSEDE: accelerating scientific discovery. *Comput. Sci. Eng.* **2014,** *16*, 62-74; (h) Zhao, Y.; Truhlar, D. G., The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008,** *120*, 215-241.