

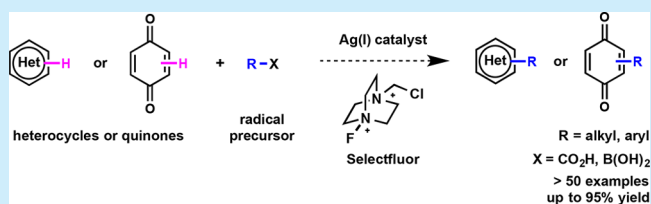
Silver-Catalyzed Minisci Reactions Using Selectfluor as a Mild Oxidant

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S Supporting Information

ABSTRACT: A new method for silver-catalyzed Minisci reactions using Selectfluor as a mild oxidant is reported. Heteroarenes and quinones both participate in radical C–H alkylation and arylation from a variety of carboxylic and boronic acid radical precursors. Several oxidatively sensitive and highly reactive radical species are successful, providing structures that are challenging to access by other means.



The pioneering work of Minisci in the 1970s demonstrated the feasibility of using alkyl carboxylic acids as radical precursors for heteroarene C–H functionalizations.¹ Since its inception, this transformation has been used extensively in the context of drug discovery, as many target molecules may be rapidly accessed through variation of either the heterocycle or carboxylic acid component.² The traditional Minisci reaction involves Ag(I)-catalyzed radical decarboxylation of alkyl carboxylic acids at elevated temperatures with inorganic persulfates ($S_2O_8^{2-}$) as oxidants. Recent work has focused on improving the scope and efficiency of Minisci-type transformations by exploring alternative radical precursors and/or mild experimental conditions. The development of the borono-Minisci reaction extended the method to include radical arylations from aryl boronic acids and trifluoroborate radical precursors (Scheme 1A).³ Utilizing heterogeneous reaction conditions, the borono-Minisci was shown to be effective for heteroarene and quinone C–H arylations at room temperature but still required superstoichiometric amounts of $S_2O_8^{2-}$, an extremely strong oxidant ($E^\circ = 2.01$ V).⁴ Recent work in the context of radical fluorination has shown that Ag(I) and Selectfluor ($E^\circ = -0.04$ V) are capable of promoting fluorination from alkyl carboxylic acids, boronic acids, and boronate esters as radical precursors (Scheme 1B).⁵ Our own previous work in this area demonstrated that C–H fluorination is possible using amino acids as radical-transfer agents.⁶ We had established that nitrogen-containing additives affected the oxidation potential of Ag(I) catalysts, and we became interested in exploring this phenomenon beyond the context of radical fluorination. Herein we report that Minisci-type processes are effective for both heterocycle and quinone alkylation and arylation using carboxylic acids and boronic acids as radical precursors and Selectfluor as a mild oxidant (Scheme 1C).

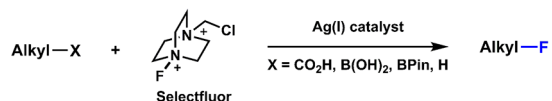
Through our work on C–H fluorination using amino acids as radical-transfer agents, we explored whether simple alkyl carboxylic acids could promote fluorination via a Ag(I)-catalyzed radical decarboxylation/hydrogen-atom transfer mechanism. Under our general conditions, no reaction was

Scheme 1. Ag(I)-Catalyzed Radical Initiations from Carboxylic and Boronic Acids

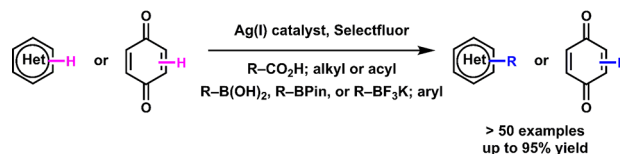
A) Traditional Minisci and Borono-Minisci Reactions



B) Selectfluor as an Oxidant for Radical Fluorinations



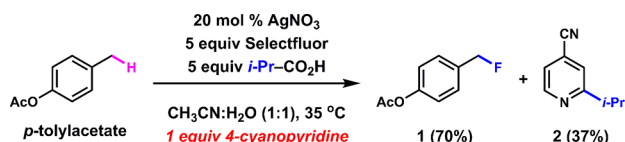
C) Minisci Reactions using Selectfluor as an Oxidant (This Work)



observed using isobutyric acid alone as a radical precursor for the C–H fluorination of *p*-tolylacetate (Scheme 2). In situ reaction monitoring using ReactIR confirmed that no Selectfluor is consumed under these conditions, suggesting that radical decarboxylation does not occur.⁷ However, the addition of 4-cyanopyridine enabled Ag(I)-catalyzed radical decarboxylation. In addition to the expected benzylic fluorination product 1, we also observed significant amounts of monoalkylated Minisci product 2. Only trace amounts of 2-fluoropropane were observed via ¹⁹F NMR, suggesting that

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Scheme 2. Discovery of Minisci Reactivity with Selectfluor^a

^aReaction conditions: *p*-tolyl acetate (0.2 mmol), Selectfluor (1.0 mmol), isobutyric acid (1.0 mmol), 4-cyanopyridine (0.2 mmol), AgNO₃ (0.04 mmol), 2 mL of CH₃CN/H₂O (1:1). Yields determined by ¹H NMR compared to 1,3,5-trimethoxybenzene as an internal standard.

isopropyl radical addition to an electron-deficient heterocycle is favored over direct fluorination via Selectfluor.⁸

Based on the results shown in Scheme 2, we became interested in exploring Minisci-type reactivity using Selectfluor as a mild oxidant. In our optimization studies, we found that 20 mol % of AgNO₃, 2.0 equiv of isobutyric acid, 2.0 equiv of Selectfluor, 1.0 equiv of trifluoroacetic acid, and a 1:1 mixture of DCE/H₂O (0.1 M) at 50 °C were suitable conditions to produce 2 in good yield (58%, Table 1, entry 1). The reaction

Table 1. Optimization of Heterocycle Alkylation

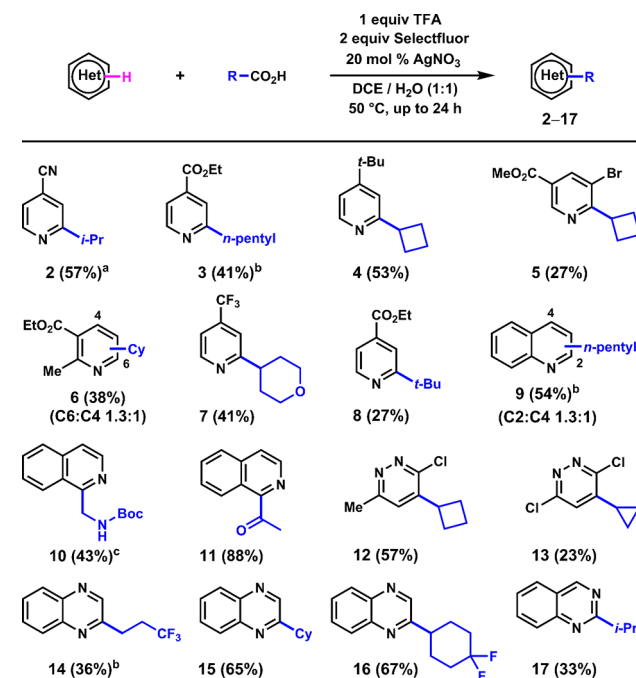
entry	deviation from standard conditions	yield of 2 (2a) ^a (%)
1	none	58 (5)
2	room temperature	53 (7)
3	no TFA	37 (1)
4	acetone instead of DCE	20 (5)
5	CH ₃ CN instead of DCE	31 (7)
6	5 equiv of isobutyric acid	59 (4)
7	(NH ₄) ₂ S ₂ O ₈ instead of Selectfluor	22 (55)
8	no AgNO ₃	0 (0)
9	no Selectfluor	0 (0)

^aYields determined by ¹H NMR using 4-methylanisole as an internal standard. General reaction conditions: 4-cyanopyridine (0.2 mmol), isobutyric acid (0.4 mmol), trifluoroacetic acid (TFA, 0.2 mmol), Selectfluor (0.4 mmol), AgNO₃ (0.04 mmol), 2 mL of DCE/H₂O (1:1), 50 °C for up to 24 h.

may be run at ambient temperature (entry 2), but heating to 50 °C was found to be generally optimal across the scope of heterocycles and carboxylic acids examined. Conversion dropped in the absence of trifluoroacetic acid, confirming that protonation of the heterocycle enhances electrophilicity (entry 3). Homogeneous solvent conditions were also explored but consistently led to lower conversion (entries 4 and 5). Increased concentration of isobutyric acid did not have a significant effect on overall conversion to 2 (entry 6), although subsequent heterocycles were shown to be sensitive to acid concentration (see Scheme 3). Standard Minisci conditions using ammonium persulfate as an oxidant led predominately to bis-alkylation (entry 7), a common problem for alkyl radical additions to very reactive heterocycles.⁹ Finally, control reactions showed that both AgNO₃ and Selectfluor are required for alkylation (entries 8 and 9).

With optimized experimental conditions established, the scope of heterocycle alkylation was explored. As shown in

Scheme 3. Scope of Heterocycle Alkylation*

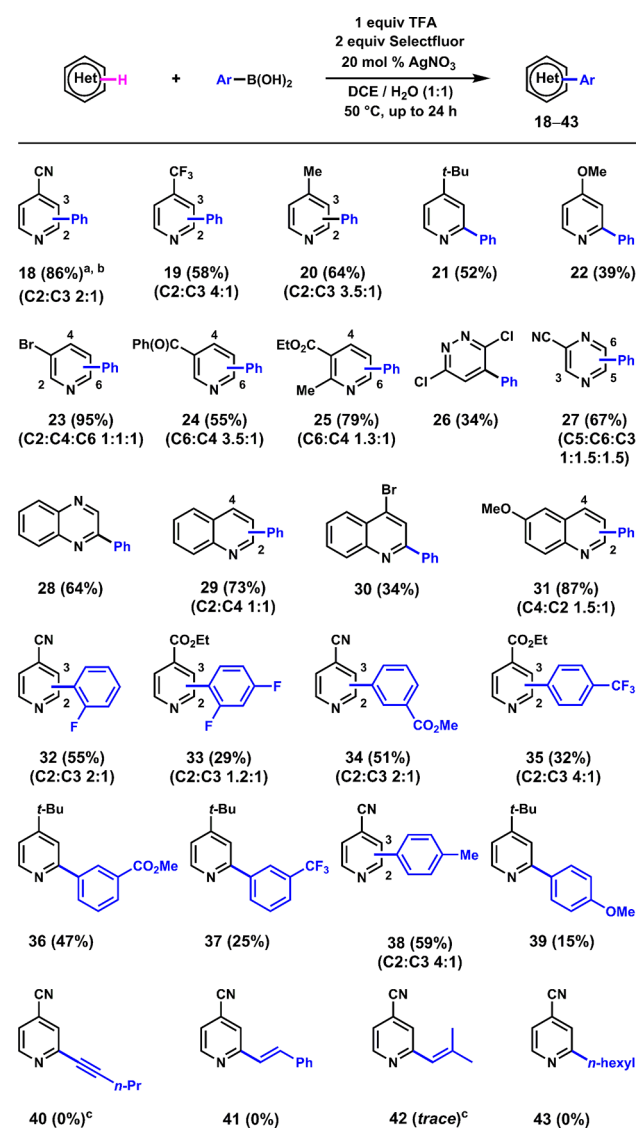


*General reaction conditions: heterocycle (0.2 mmol), carboxylic acid (0.4 mmol), trifluoroacetic acid (0.2 mmol), Selectfluor (0.4 mmol), AgNO₃ (0.04 mmol), 2 mL of DCE/H₂O (1:1), 50 °C for up to 24 h. Yields refer to chromatographically pure material unless otherwise noted. Regioisomeric ratios determined by crude ¹H NMR. ^a4% of 2,6-bis alkylated product 2a observed. See the Supporting Information for details. ^b1.0 mmol of carboxylic acid used. ^cAcetone/H₂O was used as solvent.

Scheme 3, several heterocycles and carboxylic acid radical precursors participated in our Minisci-type protocol. In most cases, unreacted heterocycle accounted for the mass balance of incomplete reactions. Pyridines, quinoline, isoquinoline, pyridazines, quinoxaline, and quinazoline were all suitably alkylated. Secondary alkyl radicals typically provide the highest yield, although primary (3, 9, 10, 14), tertiary (8), and acyl (11) radicals are also effective. Notably, *N*-protected amino acids are suitable radical precursors (10), in spite of α -aminoalkyl radicals being highly reducing and prone to overoxidation.¹⁰ It has been reported that fluorinated carboxylic acids are traditionally unsuccessful as radical precursors for Minisci reactions with heterocycles, a shortcoming that has recently been addressed using custom fluorinated sulfinate salts or alkyltrifluoroborates as alternative radical precursors.¹¹ However, we found that 4,4,4-trifluorobutyric and 4,4-difluorocyclohexane carboxylic acid are effective radical precursors under our reaction conditions, producing 14 and 16 in moderate to good yields.

In addition to alkyl carboxylic acids, aryl boronic acids serve as excellent radical precursors for heterocycle functionalizations. As shown in Scheme 4, pyridines, quinoxaline, and quinolines are all successfully arylated using phenylboronic acid as a radical precursor. Consistent with previous reports, heterocycles possessing electron-withdrawing groups are good electrophiles for reaction with nucleophilic aryl radicals (18, 19). However, we were pleased to find that electron-rich heterocycles are also suitably arylated (20–22). In addition to boronic acids, radical arylation is effective for pinacol esters and

Scheme 4. Scope of Heterocycle Radical Arylation*



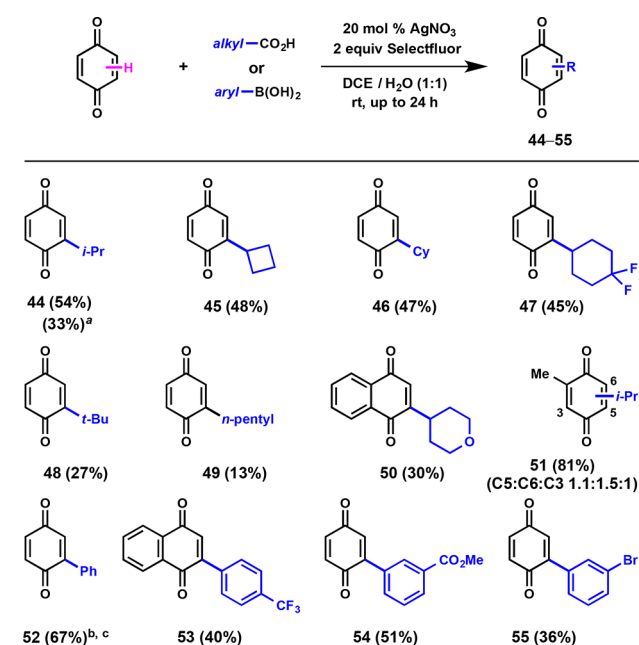
*General reaction conditions: heterocycle (0.2 mmol), phenylboronic acid (0.4 mmol), trifluoroacetic acid (0.2 mmol), Selectfluor (0.4 mmol), AgNO₃ (0.04 mmol), 2 mL of DCE/H₂O (1:1), 50 °C for up to 24 h. Yields refer to chromatographically pure material unless otherwise noted. Regioisomeric ratios determined by crude ¹H NMR. ^a50% yield (C2:C3 1.5:1) when pinacol ester used. ^b54% yield when trifluoroborate salt used (C2/C3 2.5:1). ^cPinacol ester used.

trifluoroborate salts, with these precursors producing **18** in 50% and 54% yield, respectively.

A variety of arylboronic acids and esters are suitable radical precursors for heterocycle arylation. Substitution with either electron-withdrawing (32–37) or electron-donating (38, 39) groups is tolerated. Previous reports have shown that tolyl- and methoxyboronic acids are highly reactive toward radical arylation of heterocycles, although we observe competing C–H fluorination under our reaction conditions. Alkynyl (**40**) and alkenyl (**41**, **42**) radical precursors do not appear to be effective, yielding only trace product with 4-cyanopyridine. Interestingly, although linear alkyl carboxylic acids are suitable radical precursors for heterocycle alkylation (Scheme 3, 3), *n*-hexyl boronic acid did not yield alkylated products with 4-cyanopyridine (**43**).

Several natural and synthetic quinone structures possess high degrees of biological activity.¹² Even very simple alkyl-substituted quinones, such as thymoquinone, display an impressive range of medicinal applications.¹³ Although limited examples of quinone radical alkylation are known, general methods for radical C–H alkylation of simple quinones are uncommon.¹⁴ Using Selectfluor as an oxidant, moderate to good yields are observed for Ag(I)-catalyzed quinone alkylation and arylation at room temperature (Scheme 5). Secondary

Scheme 5. C–H Alkylation and Arylation of Quinones*



*General reaction conditions: quinone (0.2 mmol), radical precursor (0.4 mmol), Selectfluor (0.4 mmol), AgNO₃ (0.04 mmol), 2 mL of DCE/H₂O (1:1), up to 24 h. Yields refer to chromatographically pure material unless otherwise noted. ^a(NH₄)₂S₂O₈ (0.4 mmol) used as an oxidant. See the Supporting Information for details. ^b63% yield when pinacol ester used. ^c61% yield when trifluoroborate salt used.

radicals are effective for alkylating *p*-benzoquinone (**44–47**), although tertiary (**48**) and primary (**49**) alkyl radicals led to poor conversion. Naphthoquinones (**50**) are successfully alkylated, and thymoquinone (**51**) can be readily accessed in one step from methyl *p*-benzoquinone using isobutyric acid as a radical precursor. Whereas high levels of monoalkylation are observed using Selectfluor as an oxidant, in our hands alkylation using traditional Minisci conditions led to low yields of **44** (33%) in addition to bis-alkylated products.⁷ Quinones have shown high levels of reactivity toward aryl radicals for C–H functionalization. In competition studies, quinones outcompete electron-deficient heteroarenes for trapping tolyl radicals, and high yields of C–H arylated products have been observed for borono-Minisci reactions.¹⁵ Under our conditions, phenylboronic acid is an efficient radical precursor for *p*-benzoquinone arylation (**52**). Similar to heterocycle arylation, boronic acid pinacol esters and trifluoroborate salts are also effective aryl radical precursors. Substituted arylboronic acids are also successful radical precursors for *p*-benzoquinone arylation (**53–55**).

In summary, we have developed a synthetic method that utilizes catalytic Ag(I) and Selectfluor as a general reagent

system to alkylate and arylate heteroarenes and quinones. Mild reaction conditions yield high levels of monoselectivity for heteroarene and quinone alkylations, and allow reactions with sensitive radical precursors. Arylation of heteroarenes and quinones is also effective from a variety of arylboronic acid radical precursors. Ongoing work in this area involves expanding the scope of substrates and radical precursors that participate in C–H functionalization. In addition, mechanistic work is underway to identify fundamental reactivity differences between the traditional Minisci reaction and one involving Selectfluor as an oxidant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b02706](https://doi.org/10.1021/acs.orglett.7b02706).

Detailed experimental procedures, full characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For the seminal contribution from Minisci and co-workers, see: (a) Minisci, F.; Bernardi, R.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575–3579. For subsequent reports by Minisci, see: (b) Minisci, F. *Synthesis* **1973**, *1973*, 1–24. (c) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489–519. (d) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycl. Chem.* **1990**, *27*, 79–96. For a selected review on the Minisci reaction, see: (e) Harrowven, D. C.; Sutton, B. J. *Prog. Heterocycl. Chem.* **2005**, *16*, 27–53.
- (2) For a review of Minisci reactions with pharmaceutically relevant molecules, see: Duncton, M. A. *MedChemComm* **2011**, *2*, 1135–1161.
- (3) For seminal reports of the borono-Minisci reaction, see: (a) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196. (b) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292–3295. For a recent iron-catalyzed boronominisci arylation, see: (c) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2012**, *48*, 11769–11771.
- (4) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27–32.
- (5) (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214–8264. (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. (c) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640–4643. (d) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439–16443.
- (6) Hua, A. M.; Mai, D. N.; Martinez, R.; Baxter, R. D. *Org. Lett.* **2017**, *19*, 2949–2952.
- (7) See the [Supporting Information](#) for additional details.
- (8) Patel, N. R.; Flowers, R. A. *J. Org. Chem.* **2015**, *80*, 5834–5841.

- (9) (a) Mai, D. N.; Baxter, R. D. *Org. Lett.* **2016**, *18*, 3738–3741. (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95–99.

(10) For oxidation potentials of α -aminoalkyl radicals, see: (a) Armstrong, D. A.; Rauk, A.; Yu, D. *J. Am. Chem. Soc.* **1993**, *115*, 666–673. For Minisci reactions from α -aminoalkyl radicals derived from amino acids, see: (b) Cowden, C. J. *Org. Lett.* **2003**, *5*, 4497–4499. (c) Shore, D. G. M.; Wasik, K. A.; Lyssikatos, J. P.; Estrada, A. A. *Tetrahedron Lett.* **2015**, *56*, 4063–4066. (d) Braun, M.-G.; Castanedo, G.; Qin, L.; Salvo, P.; Zard, S. Z. *Org. Lett.* **2017**, *19*, 4090–4093. For photocatalyzed Minisci-type reactions involving sensitive α -amino- and α -oxyalkyl radicals, see: (e) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260. (f) Jin, J.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565–1569.

(11) Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851–9855. (b) Matsui, J. K.; Primer, D. N.; Molander, G. A. *Chem. Sci.* **2017**, *8*, 3512–3522.

(12) (a) Colucci, M. A.; Couch, G. D.; Moody, C. J. *Org. Biomol. Chem.* **2008**, *6*, 637–656. (b) Urgin, K.; Jida, M.; Ehrhardt, K.; Müller, T.; Lanzer, M.; Maes, L.; Elhabiri, M.; Davioud-Charvet, E. *Molecules* **2017**, *22*, 161. (c) Nasiri, H. R.; Madej, M. G.; Panisch, R.; Lafontaine, M.; Bats, J. W.; Lancaster, C. R. D.; Schwalbe, H. *J. Med. Chem.* **2013**, *56*, 9530–9541.

(13) (a) Khader, M.; Eckl, P. M. *Iran J. Basic Med. Sci.* **2014**, *17*, 950–957. (b) Worthen, D.; Ghosheh, O. A.; Crooks, P. *Anticancer Res.* **1998**, *18*, 1527–1532.

(14) (a) Fieser, L. F.; Oxford, A. E. *J. Am. Chem. Soc.* **1942**, *64*, 2060–2065. (b) Yamago, S.; Hashidume, M.; Yoshida, J.-i. *Chem. Lett.* **2000**, *29*, 1234–1235. (c) Ngwira, K. J.; Rousseau, A. L.; Johnson, M. M.; de Koning, C. B. *Eur. J. Org. Chem.* **2017**, *2017*, 1479–1488. (d) Fröhlich, T.; Ndreškajana, B.; Muenzner, J. K.; Reiter, C.; Hofmeister, E.; Mederer, S.; Fatfat, M.; El-Baba, C.; Gali-Muhtasib, H.; Schneider-Stock, R.; Tsogoeva, S. B. *ChemMedChem* **2017**, *12*, 226–234. (e) Breyer, S.; Effenberger, K.; Schobert, R. *ChemMedChem* **2009**, *4*, 761–768. For a very recent example, see: (f) Gutiérrez-Bonet, Á.; Remeur, C.; Matsui, J. K.; Molander, G. A. *J. Am. Chem. Soc.* **2017**, *139*, 12251–12258.

(15) Baxter, R. D.; Liang, Y.; Hong, X.; Brown, T. A.; Zare, R. N.; Houk, K. N.; Baran, P. S.; Blackmond, D. G. *ACS Cent. Sci.* **2015**, *1*, 456–462.