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ARTICLE

Cross-dehydrogenative coupling of ethers and amides with the tautomerizable quinazolinones, and mechanistic studies

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Cross-dehydrogenative coupling reactions have been utilized to alkylate 4(3*H*)-quinazolinones with ethers and amides, using catalytic *n*-Bu_4NI and *t*-BuOOH as oxidant. Reactions with amides represent the first examples under such conditions. Studies *via* inter- and intramolecular competitive experiments with protio and deuterio reactants, as well as radical inhibition experiments, provided mechanistic insight. Also, an understanding of the relative reactivities of ethers was obtained by pairwise competitions with 4(3*H*)-quinazolinone.

Introduction

The 4(3*H*)-quinazolinone (quinazolinone) unit, a tautomerizable moiety, is present in a variety of alkaloids and drug candidates.[1–3] Some examples of bioactive quinazolinone derivatives are shown in Fig. 1. Febrifugine and halofuginone, two compounds found in *Dichroa febrifuga* and in the common garden plant hydrangea,[4] have been ascribed a range of bioactivities. More recently, these and their derivatives have been shown to inhibit prolyl-tRNA synthase,[5] and halofugine is used as a veterinary coccidiostat. Beyond bioactive natural products, there is effort to identify new quinazoline-based drug candidates and in this context, diproqualone as well as albaconazole are examples.

Shown in the dotted box in Fig. 1 are possible tautomers of quinazolinone, which can potentially lead to reactions at more than one center. This complication has been identified in both base- and metal-mediated alkylative processes, and the complexity is further enhanced by a substituent at C2 position.[6,7] Herein, we present studies on the unknown cross-dehydrogenative coupling (CDC) reactions of quinazolinones with ethers and amides, as an attractive and concise segue to *N*-alkylation of this heterocycle. In this context, Minisci-type reactions are known, either with quinazoline as one substrate among others,[8] or as a specific substrate.[9] However, this literature holds some interesting results. In one instance, reaction of quinazolinone and 1,4-dioxane with NaN_3/PIFA in TFE, at room temperature, led to no product.[9a] In a second case, homolytic reactions of 1,4-dihydropyridine derivatives of tetrahydropyran (THP) and benzylmethyl ether with quinazolinone gave only Minisci-type products.[9b] These are shown in Scheme 1.

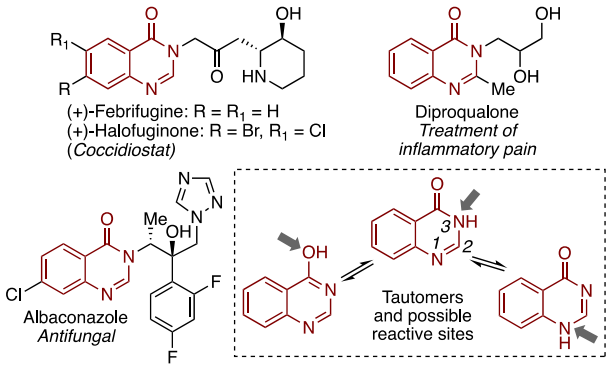
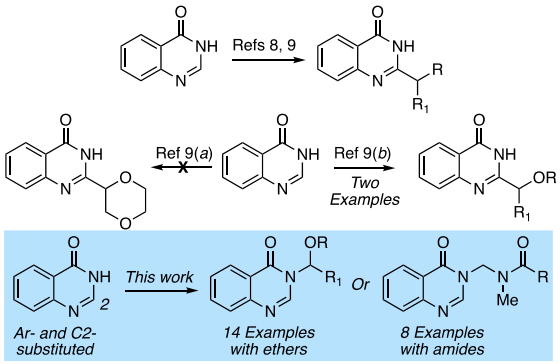


Fig. 1. Natural and synthetic biologically important quinazolinone derivatives.



Scheme 1. A summary of Minisci-type reactions of quinazolinones as well as the present work.

In the context of CDC reactions of amides, *viz.* phthalimides, saccharin as well as isothiazol-3(2*H*)-one-1,1-dioxides with ethers, use of a simple iodide salt (*n*-Bu_4NI) and a peroxide has proven successful.[10,11]

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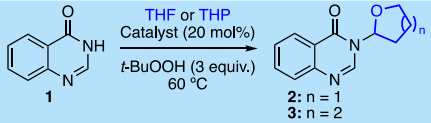
Results and discussion

These prior data were the basis for our investigations with quinazolinone and THF. In initial optimizations (Table 1), THF was first tested for reactivity with 20 mol% of *n*-Bu_4NI and 3 equiv. of *t*-BuOOH (Table 1, entries 1 and 2). The addition of MeCN as cosolvent appeared to improve the outcome slightly, but both reactions gave good yields. From the NOE and ^{13}C NMR data, the point of attachment of the THF unit was shown to be the N3 atom. The α-hydrogen atoms in the THF unit, the methine and one methylene proton (δ = 6.33 and 4.32 ppm), showed NOE correlations with the proton at C2 (δ = 8.22 ppm) but not the aryl ring protons, and the ^{13}C NMR spectrum showed a C=O resonance at δ = 160.8 ppm.

Table 1 Screening of reaction conditions[a]



Entry	Ether	Catalyst	Time	Yield[b]
1	THF	*n*-Bu_4NI	4 h	*60%*[c]
2	THF	*n*-Bu_4NI	4 h	*63%*[c,d]
3	THP	*n*-Bu_4NI	4 h	*39%*[c]
4	THP	*n*-Bu_4NI	4 h	*46%*[c,d]
5	THP	*n*-Bu_4NI	4 h	*14%*[d,e]
6	THP	$(n\text{-}Bu_4N)_2S_2O_8$	4 h	*Trace*[c,d,f]
7	THP	NH_4I	4 h	*None*[c,d,f]
8	THP	*n*-Bu_4NI	21 h	*60%*[c,g]
9	THP	*n*-Bu_4NI	21 h	*59%*[c,h]

[a] Reactions were conducted on a 0.2 mmol scale of quinazolinone, with 20 equiv. of the ether, under a nitrogen atmosphere. [b] When reported, yield is of isolated and purified product. [c] *t*-BuOOH in decane (5–6 M) was used. [d] MeCN (324 µL) was used as a cosolvent. [e] *t*-BuOOH in H_2O (70% solution) was used. [f] By TLC analysis. [g] Another 10 mol% of *n*-Bu_4NI and 2.0 equiv. of *t*-BuOOH were added after 4 h. [h] The reaction was performed under air.

Stereoelectronic effects have been shown to influence hydrogen atom abstraction from ethers by *t*-butoxyl, and C–H bond scission is faster from 5-membered rings than 6-membered ones.[12] A factor in ether bond cleavages is the dihedral angle between the *p*-type orbital on the oxygen atom and the C–H bond.[12] The rate is high when this angle small and at 90° it becomes minimum. Whereas this dihedral angle in many 5- and 6-membered ethers has been calculated to be ~30°, relief of ring strain in the former has been implicated in the faster reaction.[12] In radical chlorination of various ethers by *t*-BuOCl, THF was substantially more reactive than THP.[13] In other experiments, we have empirically observed differential reactivities of ethers. Thus, these initial conditions were tested with THP (entries 3–9). Immediately, diminution in yield was observed (entry 3) and, as with THF, addition of MeCN provided an improvement (entry 4). *t*-BuOOH in H_2O was far less effective (entry 5) and both $(n\text{-}Bu_4N)_2S_2O_8$ as well as NH_4I were ineffective (entries 6 and 7). Proceeding under the assumption that slow ether reactivity coupled with destruction of the catalyst and/or peroxide could contribute to lowered conversions, addition of a second aliquot of both and a prolonged reaction time was considered (entry 8). This change brought the yield level to that

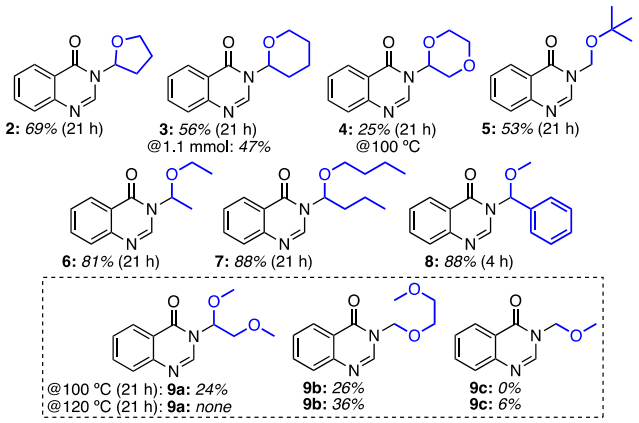


Fig. 2. Products from the reactions of quinazolinone with eight ethers.

of the THF reactions. Air did not seem to be a significant detriment at least in the one case shown (entry 9).

With the completion of these initial assessments, the scope of the reactions with respect to ethers was undertaken (Fig. 2). All these reactions were performed on the 0.5 mmol scale, and 811 µL of MeCN was used in each case. Reactions of THF and THP proceeded well, yielding products **2** and **3**. However, reaction of 1,4-dioxane was substantially inferior, yielding only 14% of product **4**. This result is consistent with its lower reactivity (only slightly better than cyclohexane) in radical chlorination.[13] The rationale provided is the presence of an oxygen atom at the β-position to the reactive center. At 100 °C, the yield from the 1,4-dioxane reaction improved. MTBE, Et_2O, and $(n\text{-}Bu)_2O$ reacted well, with the latter two providing high product yields. BnOMe was very reactive, giving a high product yield within 4 h, without additional catalyst and oxidant. Preference for reaction at the benzylic position was observed.

The reaction with DME, was interesting (see the dotted box in Fig. 2). At 100 °C, not unexpectedly, two products **9a**,**b** were observed by reaction at the 1° and 2° carbon center. However, there was not a major preference for one over the other. At 120 °C, product **9a** was not observed and the yield of isomeric **9b** increased. Unexpectedly, a minor *N*-MOM derivative **9c**, was obtained. To our knowledge, this has not been reported in reactions with DME.

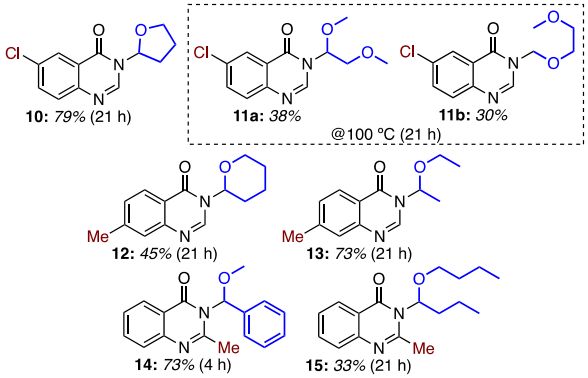
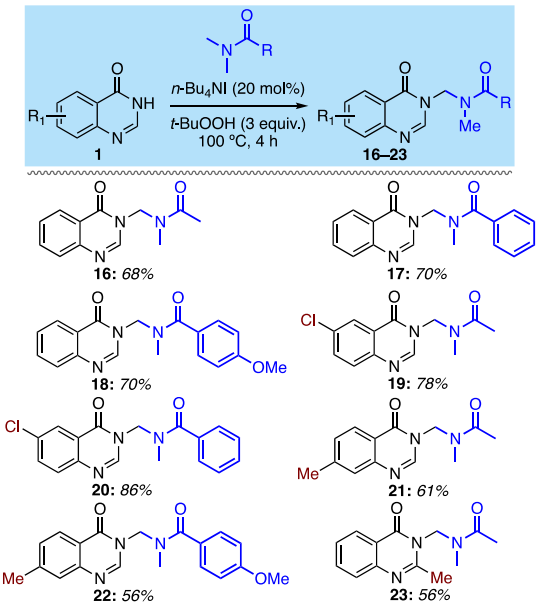


Fig. 3. Products from the reactions of substituted quinazolinones with ethers.

Next, the reactivities of 6-chloro, 7-methyl, and 2-methyquinazolinones (Fig. 3), which were prepared by known routes,[14,15] were tested. 6-Chloroquinazolinone reacted well with THF and DME, and yields were marginally higher in these cases as compared with those from quinazolinone. As expected, DME, gave two products but the yield of the product from reaction at the 2° carbon center was a little higher in this case.

Reactions of 7-methylquinazolinone with THP and Et_2O were reasonable to good, but product yields were a little lower than with quinazolinone. Finally, we tested reactions of the 2-methyl derivative, that bears a substituent proximal to the reactive center. The reaction with BnOMe proceeded well albeit in a slightly lower yield than with quinazolinone, but the reaction with $(n\text{-Bu})_2O$ was substantially lower yielding. Steric buttress proximal to the reactive centre being the likely reason.

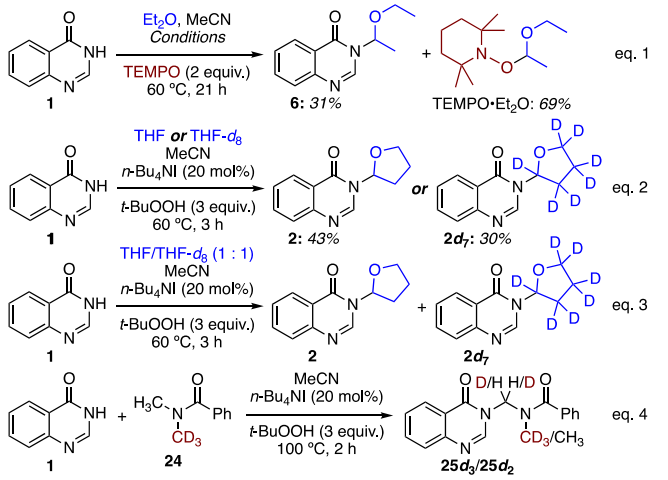
The reactions of two amides *via* this CDC process were assessed, that of quinazolinone and *N*,*N*-dimethyl amides. Initial reactions were tested at 60 and 100 °C. At the higher temperature, reactions were complete within 4 h, and without need for additional catalyst and oxidant (products in Scheme 2). Again, the lower yield obtained with 2-methylquinazolinone is likely due to unfavorable steric factors proximal to the reactive center.



Scheme 2. Products from the reactions of various quinazolinones with *N*,*N*-dimethyl amides.

In mechanistic inquiries, a radical-trapping experiment was conducted with 2 equiv. of TEMPO under the conditions utilized for the product diversification (two aliquots of the catalyst and oxidant over 21 h, Scheme 3 eq. 1). Under these conditions, the yield of product **6** decreased dramatically from 81 to 31% (based on quinazolinone), and a 69% yield of the TEMPO•Et_2O adduct was obtained (based on TEMPO). This pointed to the possible intermediacy of radical species, thus validating the relevance of the afore-described radical formation from ethers by *t*-butoxyl to this work.

Three reactions were conducted concurrently and under the same conditions; with THF, THF-d_8, and 1 : 1 THF/THF-d_8 (Scheme 3, eq. 2 and 3), and all were terminated after 3 h. Although quinazolinone (**1**) was present in each case, upon isolation it was not entirely clean in each case. The product yields from the reactions with THF and THF-d_8 were 43 and 30% respectively, indicating a slower reaction with THF-d_8. Interestingly, from the product mixture obtained from the reaction with 1 : 1 THF/THF-d_8, a reasonable assessment could not be made on the extent of reaction with each by ^{1}H NMR. This was because it appeared that almost exclusive reaction had occurred with THF (see the ESI).



Scheme 3. Reactions for the mechanistic investigations.

We did however, manage to obtain an assessment from the reaction of quinazolinone (**1**) and *N*-methyl-*N*-(trideuteriomethyl)benzamide (Scheme 3, eq. 4),[16] which was prepared from *N*-methylbenzamide and CD_3I.[17] This reaction was also terminated before completion, and the ^{1}H NMR spectrum of the product mixture **25*d*$_3$/25*d*$_2$** is shown in Fig. 4.

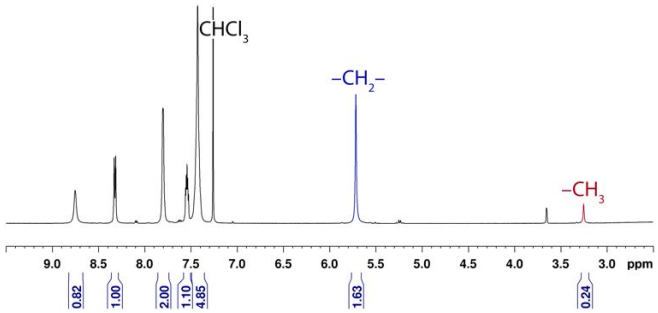
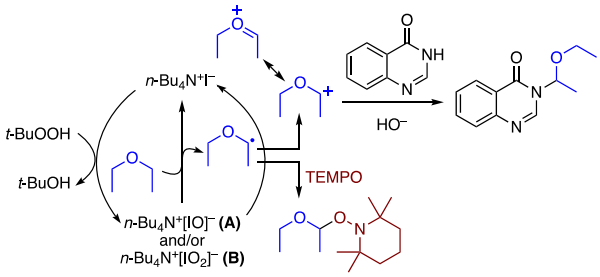


Fig. 4. The ^{1}H NMR spectrum of the mixture of **25/25*d*$_3$** (in $CDCl_3$) indicating the methyl protons from **25*d*$_2$** and the methylene protons from **25*d*$_3$**.

From this spectrum, assessment of the integration values of the CH_2 (δ = 5.72 ppm, in blue color) and CH_3 (δ = 3.24 ppm, in red color) resonances indicated a significantly greater reaction at the CH_3 than the CD_3. The ratio of **25*d*$_3$/25*d*$_2$** was estimated as ~10.2 : 1 (Fig. 5). As a comparison, this value is lower than that reported for the reaction of phthalimide (15.7 : 1)[10] but

higher than the KIE reported for the reaction of saccharin (4.0).[11] These combined results point to the possibility of C–H bond scission in a rate-limiting step.

On the basis of the observed results, a plausible mechanism is presented in Scheme 4. Oxidation of *n*-Bu_4NI by *t*-BuOOH has been shown to produce hypoiodite ($[IO]^-$) or iodite ($[IO_2]^-$),[18,19] with the formation of *t*-BuOH. These species can lead to radical formation at the α-position of the ether, a step that is dependent upon the ease of hydrogen atom abstraction. The initially formed radical can be trapped by TEMPO, as observed here (Scheme 3, eq. 1). The radical can then undergo SET with an iodonium species, resulting in a resonance-stabilized oxocarbenium ion. Hydroxide ion released in the ether oxidation steps can lead to proton abstraction from quinazolinone (quinazolinone can exhibit both amide and phenolic characteristics and, as a reference point, the predicted pK_a values for 4(3*H*)-pyrimidinone as well as the tautomeric 4-pyrimidinol are ~9).[20] The ensuing amide anion can capture the oxocarbenium ion, leading to product. Although the amide anion is resonance stabilized, the cation-trapping occurs regioselectively at the N3 atom.



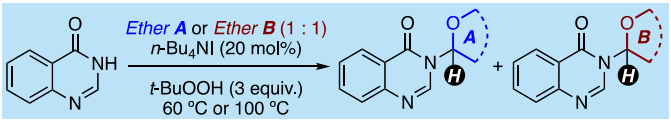
Scheme 4. A plausible mechanistic manifold with Et_2O as a representative ether.

Finally, to gain an understanding on the relative reactivities of ethers, reactions of quinazolinone (**1**) with pairs of ethers were conducted. The reaction mixtures were worked up (EtOAc/saturated aq. $Na_2S_2O_3$) and ^1H NMR data of the product mixtures were obtained. The relative amount of each product in these mixtures was estimated from the integration values of the anomeric proton resonances. From this analysis the relative reactivity order of ethers appears to be BnOMe > THF ≥ (*n*-Bu)$_2$O > Et_2O > THP > MTBE ≈ DME > dioxane.

Conclusions

This work contributes to an important area of CDC chemistry, and specifically metal-free reactions.[21–27] Herein, we have studied the *N*-alkylation of the tautomerizable 4(3*H*)-quinazolinones with ethers and amides, catalyzed by *n*-Bu_4NI and *t*-BuOOH as the oxidant. These reactions proceed by a radical pathway, likely *via* a rate-determining C–H cleavage step. Also provided are experimental results on the relative reactivities of ethers in these reactions. This work is anticipated to provide a basis for cross-dehydrogenative coupling reactions of other biologically important heterocylic systems.

Table 2 Pair-wise competitive reactions with various ethers[a]



Entry	Ethers	Temp	Time	Product ratio
1	BnOMe/THF	60 °C	1 h	3.9 : 1
2	THF/Et_2O	60 °C	1 h	1.9 : 1
3	(*n*-Bu)$_2$O/Et_2O	60 °C	1 h	1.8 : 1
4	(*n*-Bu)$_2$O/MTBE	60 °C	1 h	7.7 : 1
5	MTBE/DME	60 °C	1 h	1.1 : 1
6	THP/MTBE	60 °C	1 h	1.7 : 1
7	DME/Dioxane	60 °C	1 h	2.4 : 1
8	THF/THP	60 °C	2 h	9.3 : 1
9	THF/(*n*-Bu)$_2$O	60 °C	2 h	1.4 : 1
10	THF/MTBE	60 °C	2 h	12.9 : 1
11	THP/MTBE	60 °C	2 h	1.7 : 1
12	DME/Dioxane	100 °C	1 h	2.4 : 1

[a] Reactions were conducted on a 0.5 mmol scale of quinazolinone, with 10 equiv. of each ether, under a nitrogen atmosphere. [b] *t*-BuOOH in decane (5–6 M) was used. [c] MeCN (811 µL) was used as a cosolvent. [d] Ratio of products was obtained from the ^1H NMR data of the product mixtures, by integrating the anomeric proton resonance.

Experimental section

General experimental considerations

CH_2Cl_2, EtOAc, and hexanes were distilled over $CaSO_4$. THF, Et_2O, and 1,4-dioxane were distilled over $LiAlH_4$ and then over Na prior to use. MeCN and 1,2-DME was distilled over CaH_2. Quinazolin-4(3*H*)-one (referred to as quinazolinone), *t*-BuOOH (TBHP, 5–6 M) in decane, and other reagents were purchased from commercial sources, and were used without additional purification. 2- and 7-Methylquinazolin-4(3H)-one as well as 6-chloroquinazolin-4(3*H*)-one, all referred to as the respective substituted quinazolinones, were synthesized by known procedures.[14,15] The reaction temperatures reported are that of a sand bath, which was pre-equilibrated to the reported temperature, and then used. Thin-layer chromatography was performed on 200 µm aluminum-foil-backed silica plates and column chromatographic purifications were performed on 200–300 mesh silica gel (see individual compound descriptions). ^1H NMR spectra were recorded at 500 MHz in $CDCl_3$ or acetone-d_6 and are referenced to the residual protonated solvent resonance. ^2H NMR spectra were recorded at 77 MHz in $CHCl_3$ with a few drops of added $CDCl_3$. For this, the residual $CHCl_3$ resonance in a $CDCl_3$ sample was set to 7.26 ppm. Then the ^2H NMR spectrum of the sample prepared in $CHCl_3$ (0.5 mL) and $CDCl_3$ (3 drops) was obtained, and the D resonance of $CDCl_3$ was set to 7.24 ppm.[28] ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ or acetone-d_6 and are referenced to the solvent resonance. Chemical shifts (δ) are reported in parts per million and coupling constants (*J*) are in hertz (Hz).

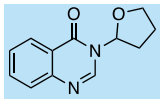
Note. We believe that products from 2-methylquinazolin-4(3H)-one are potentially more labile than the others. Not only did we see lowered yields in those cases where product isolation was possible, but we could not obtain tractable product with THF.

This contrasts with the reactions of THF with quinazolin-4(3*H*)-one and 6-chloroquinazolin-4(3*H*)-one.[29]

Representative procedure for the N-alkylation of quinazolinones with ethers and amides

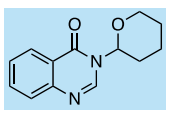
In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 73.1 mg, 0.50 mmol, 1 eq.), or 2- or 7-methylquinazolinone (80.1 mg, 0.50 mmol, 1 eq.), or 6-chloroquinazolinone (90.3 mg, 0.50 mmol, 1 eq.) in anhydrous MeCN (811.0 µL), and the appropriate ether or amide (10.0 mmol, 20.0 eq.) was added. This was followed by the addition of *n*-Bu_4NI (36.9 mg, 0.10 mmol, 0.20 equiv.), and the vial was flushed with nitrogen gas. Then, a 5.0–6.0 M solution of TBHP in decane (273.0 µL, 1.50 mmol, 3.0 equiv.) was added dropwise. The tube was capped, and the mixture was heated at 60 °C or 100 °C for 4 h. In each case the reaction was monitored by TLC after 4 h. If TLC analysis indicated complete consumption of the precursor, work up was conducted as described below. On the other hand, if TLC analysis indicated the reaction was incomplete, additional *n*-Bu_4NI (18.4 mg, 0.05 mmol, 0.10 equiv.) and 5.0–6.0 M TBHP in decane (182.0 µL, 1.00 mmol, 2.00 equiv.) were added, and the reaction was continued for a total of 21 h. The mixture was diluted with EtOAc (5.0 mL) and saturated aqueous $Na_2S_2O_3$•$5H_2O$ (5.0 mL) was added. The mixture was then transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 5.0 mL). The combined organic layer was washed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification in each case was performed by column chromatography using an appropriate eluting solvent. Details are provided under the individual compound headings.

3-(Tetrahydrofuran-2-yl)quinazolin-4(3*H*)-one (2)



The reaction with THF (811.0 µL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, followed by 30% and 50% EtOAc in hexanes gave 74.7 mg (69% yield) of product **2** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.54. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.22 (s, 1H), 7.76 (td, *J* = 7.5, 1.4 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 6.33 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.32 (td, *J* = 8.0, 4.6 Hz, 1H), 4.08 (q, *J* = 7.6 Hz, 1H), 2.59–2.51 (m, 1H), 2.18–2.07 (m, 2H), 2.05–1.97 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.8, 148.0, 142.5, 134.4, 127.5, 127.2, 126.5, 121.8, 87.4, 70.4, 33.5, 24.0. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{12}N_2NaO_2$ $[M + Na]^+$: 239.0791, found 239.0796.

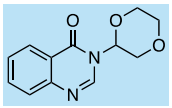
3-(Tetrahydrofuran-2*H*-pyran-2-yl)quinazolin-4(3*H*)-one (3)



The reaction with THP (978.0 µL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, followed by 30% and 50% EtOAc in hexanes gave 64.0 mg (56% yield) of product **3** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.80. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d overlapped with s, *J* = 7.9 Hz, 1H), 8.31 (singlet overlapped with d, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 5.95 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.22 (dt, *J* = 11.9, 2.0 Hz, 1H), 3.74 (td, *J* = 11.8, 2.4 Hz, 1H), 2.04 (t, *J* = 12.6 Hz, 2H), 1.83–1.67 (m, 2H), 1.66–1.58 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9, 147.7, 143.3, 134.6, 127.6, 127.3, 127.0, 121.7, 81.9, 69.5, 32.3, 25.2, 23.0. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{14}N_2NaO_2$ $[M + Na]^+$: 253.0948, found 253.0945.

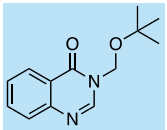
Large-scale reaction. In an oven-dried, screwcap culture tube (30 mL capacity, *ca.* 13.5 cm long × 1.2 cm wide) equipped with a stir bar, was placed quinazolinone (1, 160.8 mg, 1.1 mmol, 1.0 equiv.) in anhydrous MeCN (1.8 mL), and THP (2.1 mL, 22.0 mmol, 20.0 equiv.) was added. This was followed by the addition of *n*-Bu_4NI (81.3 mg, 0.22 mmol, 0.20 equiv.), and the vial was flushed with nitrogen gas. Then, a 5.0–6.0 M solution of *t*-BuOOH in decane (600.0 µL, 3.3 mmol, 3.0 equiv.) was added dropwise. The tube was capped, and the mixture was heated at 60 °C for 4 h, at which time TLC analysis indicated the reaction was incomplete. Thus, additional *n*-Bu_4NI (40.7 mg, 0.11 mmol, 0.10 equiv.) and 5.0–6.0 M TBHP in decane (400.0 µL, 2.2 mmol, 2.00 equiv.) were added, and the reaction was continued for a total of 21 h. The mixture was diluted with EtOAc (10.0 mL) and saturated aqueous $Na_2S_2O_3$•$5H_2O$ (10.0 mL) was added. The mixture was then transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 10.0 mL). The combined organic layer was washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, followed by 30% and 50% EtOAc in hexanes gave 119.4 mg (47% yield) of product **3** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.67. The ^{1}H NMR data of this compound matched those reported above.

3-(1,4-Dioxan-2-yl)quinazolin-4(3*H*)-one (4)



The reaction with 1,4-dioxane (852.0 µL) was heated at 100 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30%, 50% and 80% EtOAc in hexanes gave 28.8 mg (25% yield) of product **4** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.71. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 6.14 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.09 (dd, *J* = 11.4, 2.4 Hz, 2H), 4.04 (td, *J* = 11.3, 2.5 Hz, 1H), 3.86 (d, *J* = 11.7 Hz, 1H), 3.76 (td, *J* = 11.2, 2.9 Hz, 1H), 3.50 (dd, *J* = 11.2, 9.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1, 147.6, 142.9, 134.9, 127.8, 127.7, 127.1, 121.6, 78.4, 69.3, 67.4, 66.0. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{13}N_2O_3$ $[M + H]^+$: 233.0921, found 233.0917. This reaction when performed at 60 °C, over 21 h using the two aliquots of reagents gave 16.4 mg (14% yield) of product **4**.

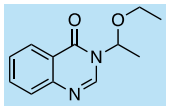
3-(*tert*-Butoxymethyl)quinazolin-4(3*H*)-one (5)



The reaction with *t*-BuOMe (1191 µL) was heated at 60 °C for 21 h, after addition of the

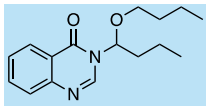
second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 62.2 mg (53% yield) of product **5** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.77. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.1 Hz, 1H), 8.25 (s, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 5.48 (s, 2H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.7, 148.0, 146.0, 134.6, 127.7, 127.5, 127.1, 122.1, 76.1, 69.1, 28.0. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{17}N_2O_2$ [M + H]$^+$: 233.1284, found 233.1280.

3-(1-Ethoxyethyl)quinazolin-4(3*H*)-one (6)



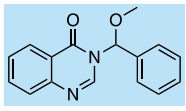
The reaction with Et_2O (1050 µL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 30% EtOAc in hexanes gave 88.4 mg (81% yield) of product **6** as a pale-yellow oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.85. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.3 Hz, 1H), 8.27 (s, 1H), 7.78 (td, *J* = 7.5, 1.4 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 6.22 (q, *J* = 6.0 Hz, 1H), 3.57–3.46 (m, 2H), 1.60 (d, *J* = 6.0 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 147.8, 142.7, 134.5, 127.6, 127.4, 126.9, 121.7, 81.1, 64.8, 22.4, 14.9. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{15}N_2O_2$ [M + H]$^+$: 219.1128, found 219.1127.

3-(1-Butoxybutyl)quinazolin-4(3*H*)-one (7)

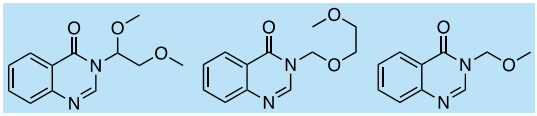


The reaction with *n*-Bu_2O (1704 µL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 30% EtOAc in hexanes gave 120.3 mg (88% yield) of product **7** as a pale-yellow oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.90. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 7.9, 0.7 Hz, 1H), 8.22 (s, 1H), 7.78 (td, *J* = 7.6, 1.4 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 6.07 (dd, *J* = 7.5, 5.4 Hz, 1H), 3.49–3.42 (m, 2H), 1.95–1.88 (m, 1H), 1.81–1.74 (m, 1H), 1.59–1.49 (m, 3H), 1.45–1.32 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1, 147.8, 143.0, 134.4, 127.6, 127.3, 127.0, 121.6, 84.4, 69.3, 38.3, 31.4, 19.3, 18.2, 13.8, 13.7. HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{22}N_2NaO_2$ [M + Na]$^+$: 297.1574, found 297.1574.

3-(Methoxy(phenyl)methyl)quinazolin-4(3*H*)-one (8)



The reaction with BnOMe (1238 µL) was heated at 60 °C for 4 h with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 117.5 mg (88% yield) of product **8** as a pale-yellow oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.78. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.04 (s, 1H), 7.78 (td, *J* = 7.6, 1.4 Hz, 1H), 7.71 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.55 (td, *J* = 7.5, 1.1 Hz, 1H), 7.48–7.47 (m, 2H), 7.40–7.35 (m, 3H), 7.16 (s, 1H), 3.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 147.7, 143.7, 137.7, 134.7, 129.1, 128.9, 127.8, 127.6, 127.2, 126.0, 121.6, 84.5, 57.1. HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{15}N_2O_2$ [M + H]$^+$: 267.1128, found 267.1128.

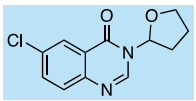


3-(1,2-Dimethoxyethyl)quinazolin-4(3*H*)-one (9a), 3-((2-methoxyethoxy)methyl)quinazolin-4(3*H*)-one (9b), and 3-(methoxymethyl)quinazolin-4(3*H*)-one (9c)

The reaction with 1,2-DME (1039 µL) was heated at 100 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 20% EtOAc in hexanes gave 27.9 mg (24% yield) of isomer **9a** as a colorless oil. Subsequent elution with 30% EtOAc in hexanes gave 30.9 mg (26% yield) of isomer **9b**, also as a colorless oil. R_f (SiO_2/50% EtOAc in hexanes): **9a** = 0.67 and **9b** = 0.54. ^{1}H NMR of isomer **9a** (500 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.26 (s, 1H), 7.79 (td, *J* = 7.5, 1.5 Hz, 1H), 7.76 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.53 (td, *J* = 8.0, 1.5 Hz, 1H), 6.15 (t, *J* = 4.4 Hz, 1H), 3.71 (qd, *J* = 12.4, 4.4 Hz, 2H), 3.43 (s, 3H), 3.40 (s, 3H). ^{13}C NMR of isomer **9a** (125 MHz, $CDCl_3$): δ = 161.4, 147.8, 143.5, 134.8, 127.8, 127.6, 127.1, 121.8, 84.0, 73.1, 59.8, 57.5. HRMS (ESI/TOF) of isomer **9a** *m/z* calculated for $C_{12}H_{15}N_2O_3$ [M + H]$^+$: 235.1077, found 235.1076. ^{1}H NMR of isomer **9b** (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 1H), 8.24 (s, 1H), 7.82–7.76 (m, 2H), 7.54 (td, *J* = 7.3, 1.6 Hz, 1H), 5.53 (s, 2H), 3.82–3.80 (m, 2H), 3.55–3.53 (m, 2H), 3.34 (s, 3H). ^{13}C NMR of isomer **9b** (125 MHz, $CDCl_3$): δ = 161.5, 148.2, 146.3, 134.9, 127.9, 127.7, 127.2, 122.2, 75.6, 71.8, 69.5, 59.2. HRMS (ESI/TOF) of isomer **9b** *m/z* calculated for $C_{12}H_{15}N_2O_3$ [M + H]$^+$: 235.1077, found 235.1076. This reaction when performed at 60 °C over 21 h, with the two aliquots of reagents, gave 16.9 mg (14% yield) of isomer **9a** and 17.5 mg (15% yield) of isomer **9b**.

This reaction was also performed at 120 °C for 21 h, with two aliquots of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 40% EtOAc in hexanes gave 5.4 mg (6% yield) of product **9c** as a white solid. Subsequent elution with 50% EtOAc in hexanes gave 42.3 mg (36% yield) of isomer **9b** as a colorless oil. R_f (SiO_2/50% EtOAc in hexanes): **9c** = 0.67 and **9b** = 0.54. ^{1}H NMR of isomer **9c** (500 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.15 (s, 1H), 7.79 (td, *J* = 7.6, 1.5 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.54 (td, *J* = 7.5, 1.2 Hz, 1H), 5.42 (s, 2H), 3.46 (s, 3H). HRMS (ESI/TOF) of isomer **9c** *m/z* calculated for $C_{10}H_{10}NaN_2O_2$ [M + Na]$^+$: 213.0634, found 213.0627.

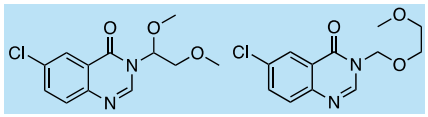
6-Chloro-3-(tetrahydrofuran-2-yl)quinazolin-4(3*H*)-one (10)



The reaction with THF (811.0 µL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 98.5 mg (79% yield) of product **10** as a white solid. R_f (SiO_2/50% EtOAc in hexanes) = 0.42. ^{1}H NMR (500 MHz,

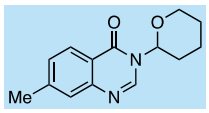
$CDCl_3$): δ = 8.25 (d, *J* = 2.2 Hz, 1H), 8.19 (s, 1H), 7.69 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 6.30 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.32 (td, *J* = 8.1, 4.5 Hz, 1H), 4.09 (td, *J* = 8.3, 6.7 Hz, 1H), 2.59–2.51 (m, 1H), 2.17–2.07 (m, 2H), 2.04–1.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0, 146.7, 142.8, 134.9, 133.2, 129.3, 126.0, 123.0, 87.7, 70.6, 33.6, 24.1. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{11}ClN_2NaO_2$ $[M + Na]^+$: 273.0401, found 273.0400.

6-Chloro-3-(1,2-dimethoxyethyl)quinazolin-4(3*H*)-one (11a) and 6-chloro-3-((2-methoxyethoxy)methyl)quinazolin-4(3*H*)-one (11b)



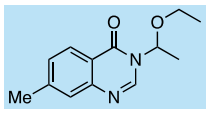
The reaction with 1,2-DME (1039 μL) was heated at 100 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 30% EtOAc in hexanes gave 51.6 mg (38% yield) of isomer **11a** as a white solid. Subsequent elution with 30% and 50% EtOAc in hexanes, and finally EtOAc gave 41.0 mg (30% yield) of isomer 11b as a white solid. R_f (SiO_2/50% EtOAc in hexanes): **11a** = 0.73 and **11b** = 0.35. ^{1}H NMR of isomer **11a** (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 2.1 Hz, 1H), 8.23 (s, 1H), 7.72 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 6.11 (t, *J* = 4.3 Hz, 1H), 3.70 (qd, *J* = 12.4, 4.4 Hz, 2H), 3.42 (s, 3H), 3.40 (s, 3H). ^{13}C NMR of isomer **11a** (125 MHz, $CDCl_3$): δ = 160.4, 146.4, 143.7, 135.1, 133.3, 129.4, 126.4, 122.8, 84.1, 72.9, 59.8, 57.5. HRMS (ESI/TOF) of isomer **11a** *m/z* calculated for $C_{12}H_{13}ClN_2NaO_3$ $[M + Na]^+$: 291.0507, found 291.0508. ^{1}H NMR of isomer **11b** (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 2.2 Hz, 1H), 8.15 (s, 1H), 7.69 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 5.49 (s, 2H), 3.79–3.78 (m, 2H), 3.53–3.51 (m, 2H), 3.33 (s, 3H). ^{13}C NMR of isomer **11b** (125 MHz, $CDCl_3$): δ = 160.5, 146.6, 146.4, 135.3, 133.7, 129.5, 126.6, 123.2, 75.7, 71.8, 69.7, 59.3. HRMS (ESI/TOF) of isomer **11b** *m/z* calculated for $C_{12}H_{14}ClN_2O_3$ $[M + H]^+$: 269.0688, found 269.0687.

7-Methyl-3-(tetrahydro-2*H*-pyran-2-yl)quinazolin-4(3*H*)-one (12)



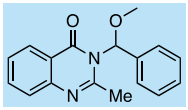
The reaction with THP (978.0 μL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 55.2 mg (45% yield) of product **12** as a pale-yellow oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.67. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.31 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.94 (dd, *J* = 10.8, 2.3 Hz, 1H), 4.21 (dt, *J* = 11.7, 2.2 Hz, 1H), 3.74 (td, *J* = 11.8, 2.5 Hz, 1H), 2.50 (s, 3H), 2.05–2.01 (m, 2H), 1.83–1.66 (m, 2H), 1.66–1.60 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9, 147.8, 145.6, 143.4, 129.0, 127.4, 126.9, 119.4, 81.8, 69.5, 32.3, 25.2, 23.1, 22.1. HRMS (ESI/TOF) *m/z* calculated for $C_{14}H_{16}N_2NaO_2$ $[M + Na]^+$: 267.1104, found 267.1103.

7-Methyl-3-(1-ethoxyethyl)quinazolin-4(3*H*)-one (13)



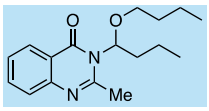
The reaction with Et_2O (1050 μL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 84.8 mg (73% yield) of product **13** as a pale-yellow oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.77. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.34 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.22 (q, *J* = 6.0 Hz, 1H), 3.56–3.45 (m, 2H), 2.52 (s, 3H), 1.59 (d, *J* = 6.0 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9, 148.0, 145.6, 142.8, 129.0, 127.4, 126.8, 119.3, 81.0, 64.8, 22.4, 22.0, 15.0. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{16}N_2NaO_2$ $[M + Na]^+$: 255.1104, found 255.1109.

3-(Methoxy(phenyl)methyl)-2-methylquinazolin-4(3*H*)-one (14)



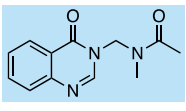
The reaction with BnOMe (1238 μL) was heated at 60 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 10% and 30% EtOAc in hexanes gave 102.8 mg (73% yield) of product **14** as a colorless oil. R_f (SiO_2/30% EtOAc in hexanes) = 0.54. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.68 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.38–7.32 (m, 5H), 3.57 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 155.0, 147.5, 138.1, 134.9, 128.8, 128.4, 127.4, 126.9, 126.8, 125.4, 120.0, 84.8, 57.1, 23.6. Whereas a good HRMS value could not be obtained for product 14, a good value was found for the hydrolysis product. It is possible that steric factors are responsible for this observation. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{17}N_2O_2$ $[M + H]^+$: 281.1284, found 281.0933. For the hydrolysis product HRMS (ESI/TOF) calculated for $C_{16}H_{15}N_2O_2$ $[M + H]^+$: 267.1128, found 267.1134.

3-(1-Butoxybutyl)-2-methylquinazolin-4(3*H*)-one (15)



The reaction with *n*-Bu_2O (1704 μL) was heated at 60 °C for 21 h, after addition of the second aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 30% EtOAc in hexanes gave 48.0 mg (33% yield) of product **15** as a colorless oil. R_f (SiO_2/50% EtOAc in hexanes) = 0.70. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.0, 1.1 Hz, 1H), 7.72 (td, *J* = 7.6, 1.4 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 6.53 (t, *J* = 5.7 Hz, 1H), 3.44 (t, *J* = 6.5 Hz, 2H), 2.77 (s, 3H), 2.15–2.08 (m, 1H), 1.88–1.81 (m, 1H), 1.58–1.52 (m, 2H), 1.45–1.25 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 162.5, 154.2, 147.5, 134.2, 126.7, 126.67, 126.1, 120.3, 85.3, 68.9, 36.5, 31.3, 22.8, 19.1, 18.8, 13.2, 13.1. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{24}N_2NaO_2$ $[M + Na]^+$: 311.1730, found 311.1740.

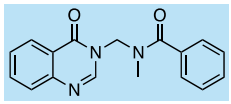
***N*-Methyl-*N*-((4-oxoquinazolin-3(4*H*)-yl)methyl)acetamide (16)**



The reaction with DMA (930.0 μL) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel

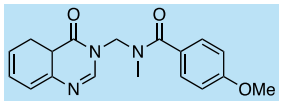
column packed in hexanes, sequentially eluted with hexanes, 50% EtOAc in hexanes, EtOAc, and 5% MeOH in EtOAc gave 79.2 mg (68% yield) of product **16** as a white solid. R_f (SiO_2/EtOAc) = 0.20. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 8.29 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (td, *J* = 7.5, 1.4 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 5.51 (s, 2H), 3.31 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 162.1, 148.3, 147.8, 134.7, 127.9, 127.4, 126.8, 122.1, 57.9, 37.8, 22.0. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{14}N_3O_2$ $[M + H]^+$: 232.1080, found 232.1080.

N-Methyl-N-((4-oxoquinazolin-3(4H)-yl)methyl)benzamide (17)



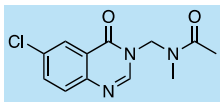
The reaction with *N,N*-dimethylbenzamide (1.492 g) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in 50% CH_2Cl_2 in hexanes, sequentially eluted with 50% and 80% CH_2Cl_2 in hexanes, CH_2Cl_2, and finally 50% EtOAc in CH_2Cl_2 gave 102.2 mg (70% yield) of product **17** as a white foam. R_f (SiO_2/20% EtOAc in CH_2Cl_2) = 0.19. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (s, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.81–7.75 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.43 (s, 5H), 5.72 (s, 2H), 3.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 161.9, 148.1, 147.6, 134.9, 134.6, 130.4, 128.5, 127.7, 127.3, 127.2, 126.7, 121.9, 57.5, 38.7. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{16}N_3O_2$ $[M + H]^+$: 294.1237, found 294.1235.

4-Methoxy-N-methyl-N-((4-oxoquinazolin-3(4H)-yl)methyl)benzamide (18)



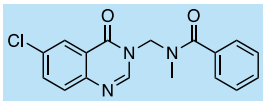
The reaction *N,N*-dimethyl-4-methoxybenzamide (1.792 g) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in 50% CH_2Cl_2 in hexanes, sequentially eluted with 50% and 80% CH_2Cl_2 in hexanes, CH_2Cl_2, and finally 50% EtOAc in CH_2Cl_2 gave 114.1 mg (70% yield) of product **18** as a yellow solid. R_f (SiO_2/EtOAc) = 0.39. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.80–7.75 (m, 2H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 5.71 (s, 2H), 3.84 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 162.0, 161.4, 148.2, 147.7, 134.8, 129.6, 128.7, 127.8, 127.5, 126.9, 122.0, 113.8, 57.8, 55.5, 38.9. One aromatic carbon resonance is not discernible, it appears like a quaternary carbon merged with another resonance δ = 126.9 ppm. HRMS (ESI/TOF) *m/z* calculated for $C_{18}H_{17}N_3NaO_3$ $[M + Na]^+$: 346.1162, found 346.1163.

N-((6-Chloro-4-oxoquinazolin-3(4H)-yl)methyl)-N-methylacetamide (19)



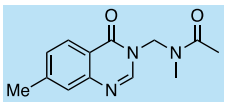
The reaction with DMA (930.0 µL) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 50% and 90% EtOAc in hexanes, EtOAc, and finally 5% MeOH in EtOAc gave 103.2 mg (78% yield) of product **19** as a white solid. R_f (SiO_2/EtOAc) = 0.20. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (s, 1H), 8.25 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 5.48 (s, 2H), 3.30 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 161.0, 148.0, 146.7, 135.0, 133.1, 129.4, 126.1, 123.1, 58.1, 37.8, 21.9. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_{13}ClN_3O_2$ $[M + H]^+$: 266.0691, found 266.0691.

N-((6-Chloro-4-oxoquinazolin-3(4H)-yl)methyl)-N-methylbenzamide (20)



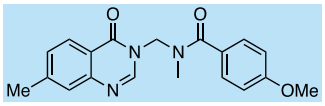
The reaction with *N,N*-dimethylbenzamide (1.492 g) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in 50% hexanes in CH_2Cl_2, sequentially eluted with 50% and 80% hexanes in CH_2Cl_2, CH_2Cl_2, and finally 50% EtOAc in CH_2Cl_2 gave 140.4 mg (86% yield) of product **20** as a pale-yellow oil. R_f (SiO_2/80% CH_2Cl_2 in EtOAc) = 0.31. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1H), 8.28 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.43 (s, 5H), 5.70 (s, 2H), 3.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 160.8, 147.8, 146.6, 134.9, 134.7, 133.1, 130.4, 129.3, 128.5, 127.2, 126.1, 123.0, 57.8, 38.8. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{15}ClN_3O_2$ $[M + H]^+$: 328.0847, found 328.0846.

N-Methyl-N-((7-methyl-4-oxoquinazolin-3(4H)-yl)methyl)acetamide (21)



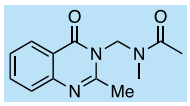
The reaction with DMA (930.0 µL) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 50% and 90% EtOAc in hexanes, EtOAc, and finally 5% MeOH in EtOAc gave 75.2 mg (61% yield) of product **21** as a pale-yellow oil. R_f (SiO_2/EtOAc) = 0.33. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 2H) 3.30 (s, 3H), 2.51 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 162.0, 148.4, 147.8, 145.8, 128.9, 127.6, 126.6, 119.7, 57.7, 37.6, 22.0, 21.9. HRMS (ESI/TOF) *m/z* calculated for $C_{13}H_{15}N_3NaO_2$ $[M + Na]^+$: 268.1056, found 268.1056.

4-Methoxy-N-methyl-N-((7-methyl-4-oxoquinazolin-3(4H)-yl)methyl)benzamide (22)



The reaction *N,N*-dimethyl-4-methoxybenzamide (1.792 g) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in 50% hexanes in CH_2Cl_2, sequentially eluted with 50% and 80% hexanes in CH_2Cl_2, CH_2Cl_2, and finally 50% EtOAc in CH_2Cl_2 gave 94.7 mg (56% yield) of product **22** as a yellow foam. R_f (SiO_2/EtOAc) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.54 (s, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.69 (s, 2H), 3.83 (s, 3H), 3.26 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 162.0, 161.5, 148.3, 147.9, 146.0, 129.6, 129.1, 127.6, 126.9, 126.7, 119.6, 113.9, 57.6, 55.5, 38.8, 22.1. HRMS (ESI/TOF) *m/z* calculated for $C_{19}H_{20}N_3O_3$ $[M + H]^+$: 338.1499, found 338.1498.

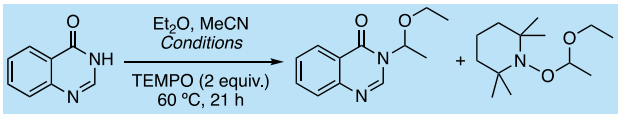
_N_-Methyl-_N_-((2-methyl-4-oxoquinazolin-3(4_H_)-yl)methyl)acetamide (23)



The reaction with DMA (930.0 µL) was heated at 100 °C for 4 h, with a single aliquot of reagents. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 50% and 90% EtOAc in hexanes, EtOAc, and finally 5% MeOH in EtOAc gave 68.2 mg (56% yield) of product **23** as a pale-yellow gum. R_f (SiO_2/ EtOAc) = 0.16. ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.20 (dd, J = 7.9, 1.1 Hz, 1H), 7.81 (td, J = 7.7, 1.2 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 5.78 (s, 2H) 3.12 (s, 3H), 2.66 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 171.1, 162.7, 155.2, 147.6, 134.3, 126.8, 126.6, 126.1, 120.5, 54.5, 34.5, 22.5, 21.3. HRMS (ESI/TOF) m/z calculated for $C_{13}H_{15}N_3NaO_2$ $[M + Na]^+$: 268.1056, found 268.1058.

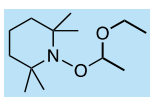
Mechanistic experiments

Reaction of quinazolinone and Et_2O in the presence of TEMPO



In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 36.5 mg, 0.25 mmol, 1.0 equiv.) in anhydrous MeCN (405.0 µL), and Et_2O (524.0 µL, 5.0 mmol, 20.0 equiv.) was added. This was followed by the addition of TEMPO (78.1 mg, 0.50 mmol, 2.0 equiv.), n-Bu_4NI (18.5 mg, 0.05 mmol, 0.20 equiv.), and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (136.0 µL, 0.75 mmol, 3.0 equiv.) was added dropwise, the tube was capped, and the mixture was heated at 60 °C for 4 h. The reaction was monitored by TLC and after 4 h, TLC analysis indicated the presence of a significant amount of precursor 1. Then additional aliquots of n-Bu_4NI (9.3 mg, 0.02 mmol, 0.10 equiv.) and 5.0–6.0 M TBHP in decane (91.0 µL, 0.50 mmol, 2.0 equiv.) were added, and the stirring was continued for 21 h. The reaction mixture was diluted with EtOAc (2.5 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 2.5 mL). The combined organic layer was washed with brine (2.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, and 10% EtOAc in hexanes gave the TEMPO•Et_2O adduct (79.8 mg, 69%) as a colorless oil. Continued elution with 30% EtOAc in hexanes gave compound **6** (16.8 mg, 31%) as a colorless oil. Further elution with 40% EtOAc in hexanes and EtOAc gave unreacted precursor **1** (9.4 mg, impure).

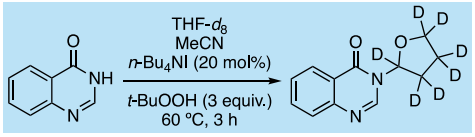
***Characterization of TEMPO•Ether adduct*[30]**



R_f (SiO_2/5% EtOAc in hexanes) = 0.55. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.87 (q, J = 5.5 Hz, 1H), 3.75 (dq, J = 9.2, 7.1 Hz, 1H), 3.57 (dq, J = 9.2, 7.0 Hz, 1H), 1.48–1.41 (m, 6H), 1.29 (d, J = 5.5 Hz, 3H), 1.23 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 105.1, 63.0, 60.6, 59.3, 40.6, 40.2, 33.9, 33.8, 20.7, 20.2, 19.4, 17.4, 15.5. HRMS (ESI/TOF) m/z calculated for $C_{13}H_{28}NO_2$ $[M + H]^+$: 230.2115, found 230.2118.

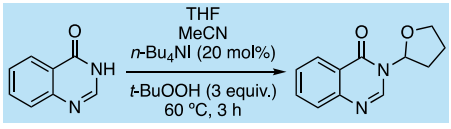
The ^{1}H NMR data for compound **6** obtained from this reaction matched those reported above.

Reaction of quinazolinone with THF-d_8



In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 36.5 mg, 0.25 mmol, 1.0 equiv.) in anhydrous MeCN (405.0 µL), and THF-d_8 (407.0 µL, 5.0 mmol, 20.0 equiv.) was added. This was followed by the addition of n-Bu_4NI (18.5 mg, 0.05 mmol, 0.20 equiv.) and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (136.0 µL, 0.75 mmol, 3.0 equiv.) was added dropwise, the vial was capped, and the mixture was heated at 60 °C for 3 h. TLC analysis indicated the presence of unconsumed precursor 1. The reaction mixture was diluted with EtOAc (2.5 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 2.5 mL). The combined organic layer was washed with brine (2.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 16.7 mg (30% yield) of product **2d_7** as a white solid. Precursor **1** (16.5 mg, impure) was reisolated. HRMS (ESI/TOF) m/z calculated for $C_{12}H_6D_7N_2O_2$ $[M + H]^+$: 224.1411, found 224.1411.

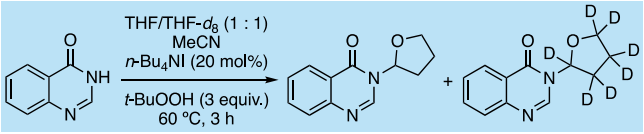
Reaction of quinazolinone with THF



In an oven-dried screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 36.5 mg, 0.25 mmol, 1.0 eq.) in anhydrous MeCN (405.0 µL) and THF (405.0 µL, 5.00 mmol, 20.0 equiv.) was added. This was followed by the addition of n-Bu_4NI (18.5 mg, 0.050 mmol, 0.20 equiv.) and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (136.0 µL, 0.75 mmol, 3.0 equiv.) was added dropwise, the tube was capped, and the mixture was heated at 60 °C for 3 h. TLC analysis indicated the presence of unconsumed precursor **1**. The reaction mixture was diluted with EtOAc (2.5 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 2.5 mL). The combined organic layer was washed with brine (2.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in

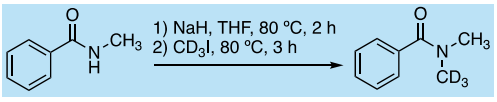
hexanes gave 23.3 mg (43% yield) of product **2** as a colorless oil. Precursor **1** (6.3 mg, pure) was reisolated.

Competitive reaction of quinazolinone with THF and THF-d_8



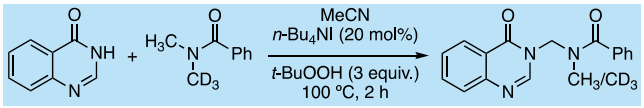
In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 36.5 mg, 0.25 mmol, 1.0 equiv.) in anhydrous MeCN (405.0 µL). To this mixture, THF (203.0 mL, 2.50 mmol, 10.0 equiv.) and THF-d_8 (203.0 µL, 2.50 mmol, 10.0 equiv.) were added. This was followed by the addition of *n*-Bu_4NI (18.5 mg, 0.05 mmol, 0.20 equiv.) and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (136.0 µL, 0.75 mmol, 3.0 equiv.) was added dropwise, the vial was capped, and the mixture was heated at 60 °C for 3 h. TLC analysis indicated the presence of unconsumed precursor 1. The reaction mixture was diluted with EtOAc (2.5 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 2.5 mL). The combined organic layer was washed with brine (2.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography of the crude material on a 200–300 mesh silica gel column packed in hexanes, sequentially eluted with hexanes, 30% and 50% EtOAc in hexanes gave 25.0 mg of the THF/THF-d_8 derived products (**2**/**2d_7**) as a white solid. Precursor **1** (13.3 mg, impure) was reisolated. HRMS (ESI/TOF) *m/z* calculated for $C_{12}H_6D_7N_2O_2$ $[M + H]^+$: 224.1411, found 224.1354 and for $C_{12}H_{13}N_2O_2$ $[M + H]^+$: 217.0972, found 217.1031.

Synthesis of *N*-methyl-*N*-(trideuteriomethyl)benzamide (24)[16]



In an oven-dried 100 mL long-necked, round bottom flask equipped with a stir bar, was placed *N*-methylbenzamide (3.27 g, 24.2 mmol, 1.0 equiv.) in THF (24.2 mL). NaH (a 60% dispersion in mineral oil, 1.16 g, 29.0 mmol, 1.2 equiv.) was added. The flask was stoppered, and the mixture was stirred at 80 °C for 2 h. After cooling the mixture to room temperature, CD_3I was added, and the stirring was resumed at 80 °C. This reaction was monitored by TLC, and after 3 h precursor 1 had been consumed. After cooling the reaction mixture over an ice-bath, the mixture was quenched with water (5 mL), transferred to a separatory funnel, and extracted with CH_2Cl_2 (5 mL). The aqueous layer was separated and back-extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in 50% hexanes in EtOAc and eluted with 50% EtOAc in CH_2Cl_2 gave 2.56 g (70% yield) of product **24** as a colorless oil. R_f (SiO_2/ 20% EtOAc in hexanes) = 0.22. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.38 (m, 5H), 3.11 and 2.97 (2s, 3H). The ^1H NMR data for compound **24** are in agreement with those previously reported.[16]

Intramolecular competitive reaction of quinazolinone with N-methyl-N-(trideuteriomethyl)-benzamide



In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 36.5 mg, 0.25 mmol, 1.0 equiv.) in anhydrous MeCN (405.0 mL), and amide **24** (0.761 g, 5.0 mmol, 20.0 equiv.) was added. This was followed by the addition of *n*-Bu_4NI (18.5 mg, 0.05 mmol, 0.20 equiv.) and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (136.0 mL, 0.75 mmol, 3.0 equiv.) was added dropwise, the tube was capped, and the mixture was heated at 100 °C for 2 h. This reaction was monitored by TLC and after 2 h, a significant amount of precursor **1** was still present. The reaction mixture was diluted with EtOAc (2.5 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 2.5 mL). The combined organic layer was washed with brine (2.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by column chromatography on a 200–300 mesh silica gel column packed in 50% hexanes in CH_2Cl_2, sequentially eluted with 50% hexanes in CH_2Cl_2, CH_2Cl_2, and 50% EtOAc in CH_2Cl_2 gave 36.2 mg (49% yield) of desired products **25d_3**/**25d_2** as a colorless oil. Precursor **1** (8.2 mg, impure) was reisolated upon continued elution with EtOAc. HRMS (ESI/TOF) *m/z* calculated for $C_{17}H_{13}D_3N_3O_2$ $[M + H]^+$: 297.1425, found 297.1425 and for $C_{17}H_{14}D_2N_3O_2$ $[M + H]^+$: 296.1363, found 296.1360.

Competitive reaction of quinazolinone with ethers

In an oven-dried, screwcap culture tube (20 mL capacity, *ca.* 14.5 cm long × 1.0 cm wide) equipped with a stir bar, was placed quinazolinone (**1**, 73.1 mg, 0.50 mmol, 1.0 equiv.) in anhydrous MeCN (811.0 µL), 1 : 1 molar mixture of ethers (10.0 mmol, 20.0 equiv.) were added. This is followed by the addition of *n*-Bu_4NI (36.9 mg, 0.10 mmol, 0.20 equiv.) and the vial was flushed with nitrogen gas. Then, 5.0–6.0 M TBHP in decane (273.0 µL, 1.50 mmol, 3.0 equiv.) was added dropwise, the tube was capped, and the mixture was heated either at 60 °C or 100 °C, for either 1 or 2 h. TLC analysis indicated these reactions to be incomplete. In each case, the reaction mixture was diluted with EtOAc (5.0 mL), saturated aqueous $Na_2S_2O_3$•$5H_2O$ (2.5 mL) was added, and the mixture was transferred to a separatory funnel for extraction. The aqueous layer was separated and back-extracted with EtOAc (2 × 5.0 mL). The combined organic layer was washed with brine (5.0 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The ^1H spectra of the crude product mixtures were analyzed to determine the relative ratio of products derived from each ether. This was done by integrating the proton at the α-position to the ether oxygen atom.

Author contributions

Conceptualization and assistance with data interpretation when needed: M.K.L.; organic synthesis, data acquisition, and interpretation: D.S.; HRMS analysis P.H.W.; article writing: M.K.L. with input from other authors; generation of the ESI: D.S.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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