Synthetic Methods

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Copper-Catalyzed Intramolecular Oxidative 6-*exo*-trig Cyclization of 1,6-Enynes with H_2O and O_2**

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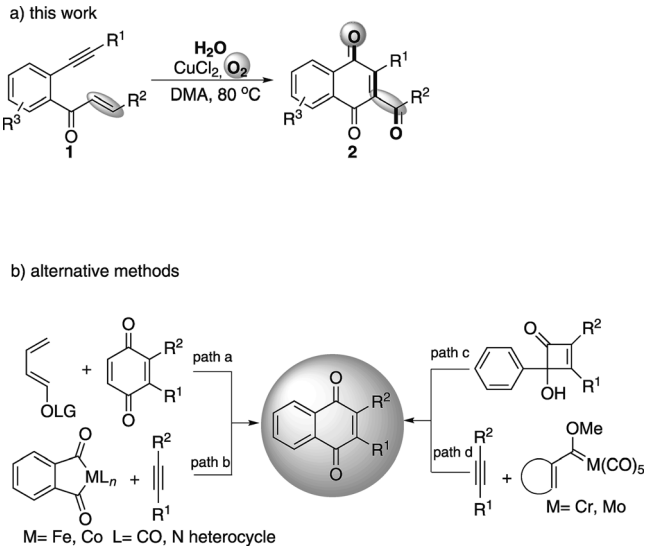
Transition-metal-catalyzed cyclization of 1,*n*-enynes has attracted significant interest because of their synthetic utility, and it is now used as a rapid and powerful approach to prepare cyclic derivatives in organic synthesis.[1–8] In particular, these cyclization transformations are highly efficient and atom economical, and provide opportunities to discover new reactions. Despite considerable progress in the field, the development of mild 1,*n*-enyne cyclization routes using inexpensive catalytic materials to construct new, complex compounds remains a challenge. Copper catalysts are widely used in organic synthesis;[2] however, examples of copper-catalyzed 1,*n*-enyne cyclizations are rare and all reports to date focus on the use of Cu^I salts.[3] The key obstacle to Cu^I catalysts is that they have a far stronger affinity for alkynes than alkenes,[2a,4a–d] which results in the addition of more nucleophilic reagents (often H_2O, amines, acids, and alcohols) rather than alkenes to alkynes.[2,4] Although this obstacle does not favor the classical 1,*n*-enyne cyclization reaction, it may facilitate 1,*n*-enyne cyclizations that include the simultaneous introduction of other more nucleophilic reagents and alkenes to alkynes. After a series of trials, we found that $Ce(SO_4)_2$ facilitated $CuCl_2$-catalyzed oxidative 6-*exo*-trig cyclization of enynes with H_2O for preparing 1,4-naphthoquinones using O_2 as an oxidant and a reactant under mild reaction conditions (Scheme 1 a).[5,6] The method is the first example of using a Cu^{II} catalyst for the oxidative cyclization of enynes, in which 1,4-naphthoquinones are constructed by the incorporation of two oxygen atoms from molecular oxygen[5c] and water into the organic framework of the product.

Quinones, particularly 1,4-naphthoquinones, are valuable synthetic intermediates, and important structural units found in numerous natural products, pharmaceutical molecules (most notably Vitamin K), and functional materials (dyes and pigments).[7] The traditional route to 1,4-naphthoquinones is the oxidation of substituted naphthols, naphthyl amines, or naphthalenes.[8] However, this method often furnishes products in low to moderate yields, and has low functional group compatibility. Owing to these drawbacks, several powerful alternative methods have arisen, including (Scheme 1 b): 1) the Diels–Alder reaction of substituted 1,3-dienes with preexisting quinones (path a),[9] 2) the reaction of alkynes with metal carbonyls (path b),[10] 3) thermo cycloisomerization of cyclobutenones (path c),[11] and 4) the annulation of Fischer carbene complexes with alkynes (path d).[12] As shown in Scheme 1, we herein describe an efficient example of achieving 1,4-naphthoquinones by catalytic oxidative 6-*exo*-trig cyclization of enynes with H_2O and O_2 using a simple and inexpensive copper salt as the catalyst. (Scheme 1).



Scheme 1. Routes to substituted 1,4-naphthoquinones. DMA = dimethylacetamide, LG = leaving group.

Our investigation began with the reaction of (*E*)-3-phenyl-1-(2-(2-phenylethynyl)phenyl)prop-2-en-1-one (**1a**) with $CuCl_2$ and O_2 in THF at 80 °C; however, only a trace amount of the target 6-*exo*-trig cyclization product **2a** was observed (Table 1, entry 1).[13] Substrate **1a** could be successfully cyclized with 10 mol % $CuCl_2$ and 1 atm O_2 at 80 °C, thus affording the desired product **2a** in 42 % yield, using DMF as the solvent (entry 2). It is noteworthy that the yield is reduced to 38 % using air instead of O_2 (entry 3). The yield was increased to 60 % when the reaction was carried out in DMA

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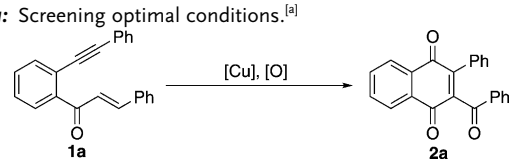
Table 1: Screening optimal conditions.[a]



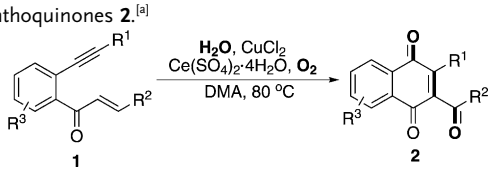
Entry	[Cu] (mol%)	Gas	Additive	*T* [°C]	Solvent	Yield [%][b]
1	$CuCl_2$ (10)	O_2	–	80	THF	trace
2	$CuCl_2$ (10)	O_2	–	80	DMF	42
3	$CuCl_2$ (10)	air	–	80	DMF	38
4	$CuCl_2$ (10)	O_2	–	80	DMA	60
5	$CuCl_2$ (10)	O_2	$K_2S_2O_8$	80	DMA	65
6	$CuCl_2$ (20)	O_2	$K_2S_2O_8$	80	DMA	67
7	$CuCl_2$ (5)	O_2	$K_2S_2O_8$	80	DMA	58
8	–	O_2	$K_2S_2O_8$	80	DMA	0
9	$CuCl_2$ (10)	Ar	$K_2S_2O_8$	80	DMA	0
10	$CuCl_2$ (10)	O_2	$K_2S_2O_8$	100	DMA	67
11[c]	$CuCl_2$ (10)	O_2	$K_2S_2O_8$	60	DMA	52
12[d]	$CuCl_2$ (20)	O_2	$K_2S_2O_8$	80	DMA	68
13	$CuCl_2$ (10)	O_2	oxone	80	DMA	63
14	$CuCl_2$ (10)	O_2	$PhI(OAc)_2$	80	DMA	60
15	$CuCl_2$ (10)	O_2	BPO	80	DMA	58
16	$CuCl_2$ (10)	O_2	*m*CPBA	80	DMA	70
17	$CuCl_2$ (10)	O_2	$(NH_4)_2Ce(NO_3)_6$	80	DMA	55
18	$CuCl_2$ (10)	O_2	$Ce(SO_4)_2{\cdot}4H_2O$	80	DMA	80
19	$CuCl_2$ (50)	O_2	–	80	DMA	56
20	$CuCl_2$ (100)	O_2	–	80	DMA	47

[a] Reaction conditions: **1a** (0.2 mmol), [Cu], gas (1 atm), additive (1.5 equiv), and solvent (3 mL) for 24 h. About 0.1% (*v*/*v*) of water is contained in solvent. [b] Yield of isolated product. [c] For 36 h. [d] **1a** (1 mmol). BPO = benzoyl peroxide; *m*CPBA = *meta*-chloroperbenzoic acid, DMF = *N*,*N*′-dimethylformamide, THF = tetrahydrofuran.

(*N*,*N*-dimethylacetamide; entry 4). In light of these results, a series of other copper catalysts, $CuBr_2$, $Cu(OTf)_2$, $Cu(OAc)_2$, and CuCl, were evaluated. Only $CuBr_2$ displayed high catalytic activity, whereas the other copper catalysts were less effective.[13] Screening revealed that the yield was enhanced slightly to 65% when 150 mol% $K_2S_2O_8$ was added (entry 5). We found that the amount of $CuCl_2$ has an effect on the reaction: the yield of **2a** using 20 mol% $CuCl_2$ was the same as when 10 mol% $CuCl_2$ was used (entry 6), but was lowered to 58% when 5 mol% $CuCl_2$ was used (entry 7). Notably, the reaction cannot take place without either Cu catalysts or O_2 (entries 8 and 9). Examination of the reaction temperature revealed that the optimal temperature was 80°C (entries 5, 10, and 11). Satisfactory yields are still obtained from the reaction of 1 mmol of substrate **1a** with $CuCl_2$, O_2, and $K_2S_2O_8$ (entry 12). Prompted by the above results, a number of other oxidative additives, such oxone, $PhI(OAc)_2$, BPO, *m*CPBA, $(NH_4)_2Ce(NO_3)_6$, and $Ce(SO_4)_2{\cdot}4H_2O$, were investigated (entries 13–18). Although five additives, oxone, $PhI(OAc)_2$, BPO, *m*CBPA, and $(NH_4)_2Ce(NO_3)_6$, displayed the same effect as $K_2S_2O_8$ (entries 13–17), $Ce(SO_4)_2$ was the most efficient and enhanced the yield to 80% (entry 18). Finally, the amount of $CuCl_2$ was tested without any additives (entries 19 and 20). The results showed yield identical to that of 10 mol% $CuCl_2$ when using 50 mol% $CuCl_2$ (entry 19), but the yield was decreased to 47% when the amount of $CuCl_2$ was enhanced to 100 mol% (entry 20).

The scope was explored under the optimal reaction conditions and the results are summarized in Table 2.[13] Initially, substituents on the aromatic moiety at the terminal alkyne were investigated: the activity of the substrates with substituents is: *para* position > *meta* position > *ortho* posi-

Table 2: $CuCl_2$-catalyzed synthesis of 1,4-naphthoquinones **2**.[a]



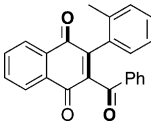
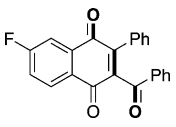
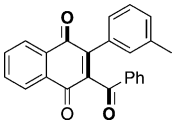
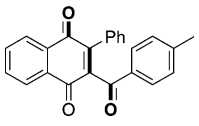
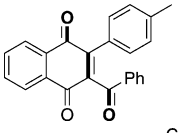
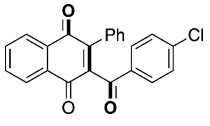
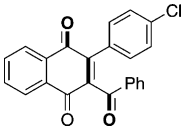
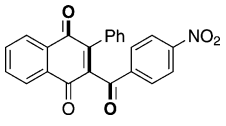
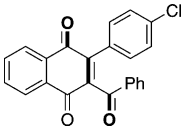
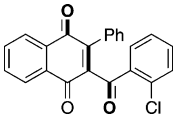
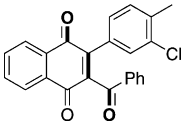
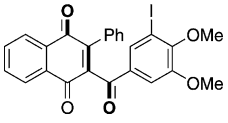
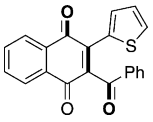
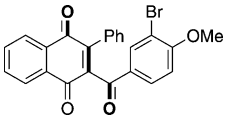
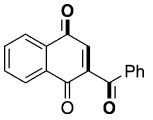
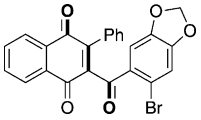
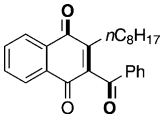
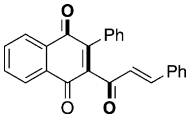
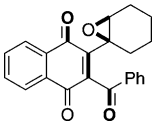
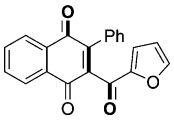
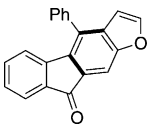
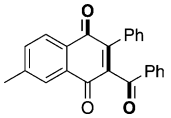
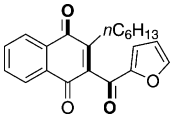
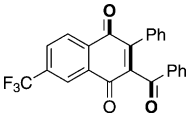
Entry	1,4-Naphthoquinone **2**		Yield [%][b]	CuCl [mol%]	*T* [°C]	*t* [h]	Entry	1,4-Naphthoquinone **2**		Yield [%][b]	CuCl [mol%]	*T* [°C]	*t* [h]
1[c]		**2b**	8	30	100	48	13		**2n**	70	10	80	24
2		**2c**	50	10	80	24	14		**2o**	75	10	80	24
3		**2d**	70	10	80	24	15		**2p**	73	30	100	30
4		**2e**	85	30	100	24	16		**2q**	63	30	100	30

Table 2: (Continued)

Entry	1,4-Naphthoquinone **2**		Yield [%][b]	CuCl [mol%]	*T* [°C]	*t* [h]	Entry	1,4-Naphthoquinone **2**		Yield [%][b]	CuCl [mol%]	*T* [°C]	*t* [h]
5		**2f**	65	50	100	24	17		**2r**	65	30	100	24
6		**2g**	80	10	80	24	18		**2s**	61	50	100	24
7		**2h**	55	10	80	24	19		**2t**	80	30	100	24
8[c]		**2i**	45	50	100	48	20		**2u**	67	50	100	24
9[c]		**2j**	50	50	100	48	21		**2v**	39	30	100	24
10[d]		**2k**	43	50	100	48	22		**2w**	36	10	80	24
									**4w**	26			
11		**2l**	76	10	80	24	23		**2x**	51	50	100	48
12		**2m**	69	10	80	24							

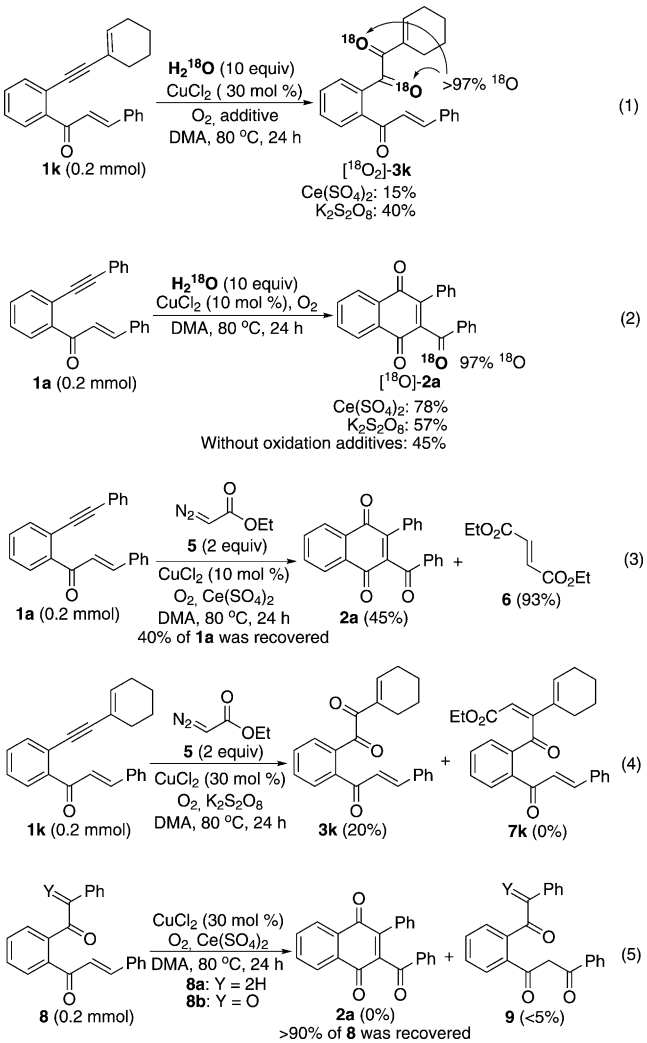
[a] Reaction conditions: **1a** (0.2 mmol), $CuCl_2$ (10 mol%), O_2 (1 atm), $Ce(SO_4)_2{\cdot}4H_2O$ (150 mol%), and DMA (0.1% *v*/*v* of water; 3 mL) at 80°C. [b] Yield of isolated product. [c] Substrate was consumed completely, and some unidentified products were observed by GC/MS analysis. [d] A by-product, (*E*)-1-(2-cinnamoylphenyl)-2-cyclohexenylethane-1,2-dione (**3k**), was isolated in 16% yield.

tion. While substrates bearing an *ortho*- or *meta*-methyl group were treated with $CuCl_2$, O_2, and $Ce(SO_4)_2$ to afford the corresponding 6-*exo*-trig cyclization products **2b** and **2c** in low to moderate yields, the substrate with a *para*-methyl group provided the desired product **2d** in a good yield. Other substituents, such as Cl and NO_2 groups, were found to be tolerated under the optimal conditions (**2e–2g**). Notably, the thiophen-2-yl-substituted substrate successfully underwent the annulation reaction with $CuCl_2$, O_2, and $Ce(SO_4)_2$ in moderate yield (**2h**). Moderate yields were found to be still achievable from terminal alkynes, aliphatic alkynes, and enynes under the same reaction conditions (**2i–2k**). By using (*E*)-1-(2-ethynylphenyl)-3-phenylprop-2-en-1-one (a terminal alkyne), for instance, the cyclization reaction proceeded smoothly to form the corresponding 2-benzoylnaphthalene-1,4-dione (**2i**) in 45% yield. Suprisingly, treatment of (*E*)-1-(2-(cyclohexenylethynyl)phenyl)-3-phenylprop-2-en-1-one, bearing a cyclohexenyl group, with $CuCl_2$, O_2, and $Ce(SO_4)_2$ afforded the cyclization/cyclohexenyl epoxidation product **2k** in 43% yield together with a by-product, (*E*)-1-(2-cinnamoylphenyl)-2-cyclohexenylethane-1,2-dione (**3k**), in 16% yield.[14] Substrates with substituents such as Me, CF_3, and F, on the aromatic ring adjacent to a ketone were also suitable for the reaction (**2l–2n**). For example, an F-substituted substrate furnished the desired product **2n** in 70% yield. The results disclosed that several functional groups, such as methyl, chloro, nitro, methoxy, iodo, and bromo groups on the aryl ring at the terminal prop-

2-en-1-one were perfectly compatible with the optimal conditions, affording the corresponding products **2o–2u** in moderate to good yields.

Importantly, the chloro, iodo, and bromo substitutions (**2p** and **2r–2u**) can be tolerated in this annulation reaction, thereby facilitating additional modifications at the halogenated positions. Moreover, some heterocycles (**2u**, **2w**, and **2x**) or olefins (**2v**) were introduced into this system, which also makes this methodology more useful for the preparation of pharmaceuticals and natural products.[15] Interestingly, another 5-*exo*-dig cyclization product **4w** was isolated from the reaction of (*E*)-3-(furan-2-yl)-1-(2-(phenylethynyl)-phenyl)prop-2-en-1-one besides the desired product **2w**. However, aliphatic alkyne only furnished the 6-*exo*-trig cyclization product **2x** in 51% yield. The reason may be that the vinylfuran moiety is highly active, thus resulting in the occurrence of a Diels–Alder reaction with arylalkynes in the presence of Lewis acids.[16]

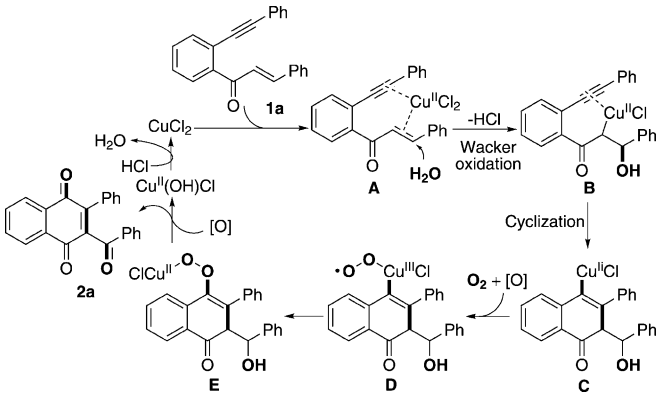
To elucidate the mechanism, some control experiments were carried out (Scheme 2).[13] It was surprising to find that the reaction of substrate **1k** with $H_2{}^{18}O$, $CuCl_2$, an additive ($Ce(SO_4)_2$ or $K_2S_2O_8$), and O_2 afforded the diketone product



Scheme 2. Control experiments.

$[^{18}O_2]$-**3k** containing two ^{18}O atoms [Eq. (1)].[14] Unfortunately, the product $[^{18}O_2]$-**3k** could not be converted into the desired cyclization product under standard conditions. It was interesting to disclose that the reaction of substrate **1a** with 10 equivalents of $H_2{}^{18}O$, $CuCl_2$, and O_2 furnished the ^{18}O-atom-containing product [^{18}O]-**2a** as determined by GC/MS and HRMS (ESI) analysis in the presence/absence of additives [Eq. (2)]. The results reveal the source of two new oxygen atoms in product **2**: one oxygen atom is from water through a Wacker-type oxidation reaction,[14] and the other oxygen atom is from O_2.[5b] Moreover, the oxygen atom of the 2-benzoyl moiety is from H_2O according to authoritative ^{13}C NMR spectra of products **2a** and [^{18}O]-**2a**.[17] The reaction between substrates **1a** and ethyl 2-diazoacetate (**5**) was carried out to examine whether the copper carbene intermediate exists:[18] only product **2a** (45% yield) together with product **6** (93% yield) were obtained [Eq. (3)]. The carbene product **7k** was not observed from the reaction of **1k** with **5** [Eq. (4)]. The cyclization reactions of substrates **8**, either (*E*)-3-phenyl-1-(2-(2-phenylacetyl)phenyl)prop-2-en-1-one or (*E*)-1-phenyl-2-(2-(3-phenylacryloyl)phenyl)ethane-1,2-dione, did not take place under the optimal reaction conditions and only a trace of olefin Wacker oxidation products **9** was observed [Eq. (5)], thus indicating that the reaction does not include the alkyne hydrolysis.[14,19] Notably, a stoichiometric amount of two radical inhibitors, TEMPO or 1,1-diphenylethene, were also tested with substrate **1a**: greater than 90% of **1a** was recovered together with a trace of target product **2a**, thereby suggesting that the reaction proceeds through a radical process.

Consequently, a possible mechanism as outlined in Scheme 3 is proposed.[1,2,4,5] Complexation of $CuCl_2$ with substrate **1a** yields the intermediate **A**, followed by sequential Wacker oxidation of the C–C double bond with H_2O (intermediate **B**)[14] and intramolecular cyclization to afford intermediate **C**. Oxidation of intermediate **C** with O_2 leads to the peroxycopper(III) intermediate **D** with the aid of the oxidative additive.[5] Reductive elimination of intermediate **D** gives rise to the formation of the peroxycopper(II) complex **E**.[5] Finally, the O–O bond cleavage of the peroxycopper(II) complex **E** and oxidization of the alcohol delivers the desired product **2a** and Cu(OH)Cl. The active Cu^{II} species can be regenerated by the reaction of Cu(OH)Cl with HCl.



Scheme 3. Possible mechanism.

There are at least two roles of the oxidative additives in this oxidation cyclization including a) oxidation of intermediate **C** to the Cu^{III} intermediate **D** and b) oxidation of the alcohol to the ketone in intermediate **E**.

In summary, we have described that inexpensive $CuCl_2$ can catalyze the intramolecular oxidative carbocyclization of (*E*)-3-aryl-1-(2-(arylethynyl)aryl)prop-2-en-1-ones with high substituent compatibility using O_2 as both the terminal oxidant and a reactant. The present method proceeds by a 6-*exo*-trig cyclization process, which provides a new approach that differs from the classical enyne cyclization method (generally by a 5-*exo*-dig cyclization).[1] Moreover, the mechanism was discussed according to the ^{18}O-labeling experiments and the results presented. Applications of this copper-catalyzed oxidative transformation in organic synthesis are currently underway in our laboratory.

Experimental Section

Typical experimental procedure for the $CuCl_2$-catalyzed intramolecular oxidative cyclization of alkynes with alkenes: (*E*)-3-aryl-1-(2-(2-arylethynyl)phenyl)prop-2-en-1-one **1** (0.2 mmol), $CuCl_2$ (10 mol%), $Ce(SO_4)_2{\cdot}4H_2O$ (150 mol%), and DMA (3 mL) were added to a Schlenk tube. The tube was then charged with O_2 (1 atm), and the reaction mixture stirred at 80°C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC and GC/MS analysis. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted in ethyl acetate, and washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 4:1) to afford the desired product **2**.

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