ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Synthesis of Unsymmetrical Ketones Using Chelation-Controlled Sequential Substitution of *N*-Triazinylamide/Weinreb Amide by Organometallic Reagents

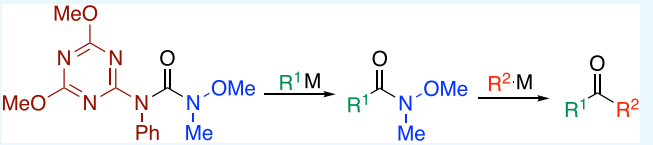
Shotaro Hirao,* Rumi Saeki, Toru Takahashi, Kento Iwai, Nagatoshi Nishiwaki, and Yasushi Ohga

Cite This: *ACS Omega* 2022, 7, 48476−48483

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: *N*-(2,4-Dimethoxy-1,3,5-triazinyl)amide was found to exhibit similar behavior to *N*-methoxy-*N*-methylamide (Weinreb amide) but higher reactivity for nucleophilic substitution by organometallic reagents. Triazinylamide suppresses overaddition, leading to the formation of a tertiary alcohol by the chelating ability of the triazinyl and carbonyl groups. Ureas possessing both triazinylamino and methoxy(methyl)amino groups underwent sequential nucleophilic substitution with different organometallic reagents, which furnished unsymmetrical ketones without any detectable tertiary alcohols.



INTRODUCTION

Grignard and organolithium reagents have been widely used for the synthesis of alcohols via nucleophilic addition to aldehydes or ketones. Ketones are not readily obtained when these reagents are subjected to reactions with acid derivatives such as esters and amides because ketones are more reactive than the acid derivatives, and undergo overaddition to afford tertiary alcohols. For the direct synthesis of ketones by nucleophilic substitution, electron-deficient or sterically hindered esters/amides are used as substrates.[1] Nucleophilic substitution of an aromatic pyrrolyl group with organometallic reagents also yields ketones.[2] Another effective approach involves stabilization of the adduct intermediate by chelation, and is a common method in modern organic syntheses, furnishing a ketone without overaddition. An amide possessing an *N*-methoxy-*N*-methylamino (MMA) group called the Weinreb amide is a representative (Figure 1, upper).[3] Other chelating groups such as carbonyl,[4] imino,[5] and sulfonyl[6] groups were found to stabilize the adduct intermediates leading to ketones; however, the amides used in most reactions are limited to cyclic amides (lactams and imides). Recently, it was demonstrated that the 1-pyrazolyl group is a good leaving group in the synthesis of ketones using Grignard reagents.[7]

Although these protocols are useful, the synthesis of unsymmetrical ketones via sequential nucleophilic substitution using different organometallic reagents is still a challenge. Sarpong et al. focused on the leaving ability of the azolyl group and successfully synthesized unsymmetrical ketones using a combination of 1-pyrrolyl and MMA groups.[8,9] In this reaction the substrate serves as a dicationic C1 unit to afford unsymmetrical ketones in one pot by successive nucleophilic substitution with different organometallic reagents. With regard to the successive chelation-controlled ketone synthesis, three protocols were reported. Symmetrical urea (bis-Weinreb amide) reacts with Grignard and organolithium reagents; however, in situ elimination does not proceed; thus, two-step reactions are necessary for synthesizing unsymmetrical ketones.[10,11] Unsymmetrical urea (*N*-methoxy-*N*,*N*′,*N*′-trimethylurea) reacted with only organolithium reagents to afford a mixture of two amides, *N*,*N*-dimethylamide and Weinreb amide, and the former amide suffers from poor electrophilicity in the second nucleophilic substitution.[11] *N*-Methoxy-*N*-methyl-*O*-(2-pyridyl)urethane facilitates the synthesis of unsymmetrical ketones; however, selectivity is not so high because of the similar coordinating ability between Weinreb amide and the 2-pyridyl group.[12] Hence, selective one-pot

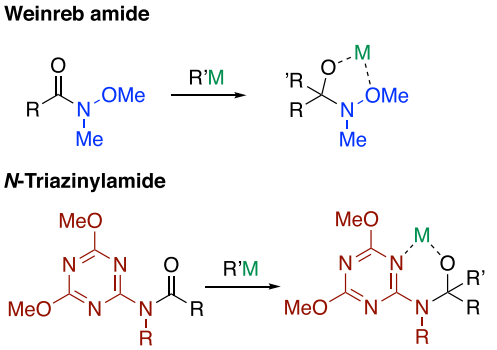


Figure 1. Stabilized intermediates by the chelating effect.

Received: October 20, 2022
Accepted: November 23, 2022
Published: December 15, 2022

ACS Publications

© 2022 The Authors. Published by American Chemical Society

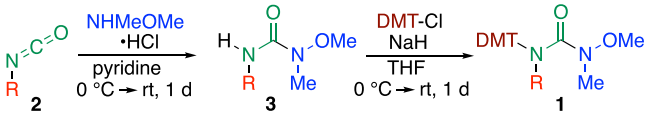
synthesis of unsymmetrical ketones using chelation-controlled sequential substitution has not been successfully established.

The historical background suggests that nucleophilic substitution is possible on the carbonyl group of an amide by a carbon nucleophile if a substituent with both coordinating and leaving abilities is introduced to the nitrogen atom. From this viewpoint, our attention focused on the 2,4-dimethoxy-1,3,5-triazinyl (DMT) group for two reasons: (1) the ring nitrogen of the DMT group stabilizes the adduct intermediate by forming a six-membered chelate complex to suppress overaddition and (2) the bulkiness of the triazine ring extends the bond length of the adjacent C═O bond and decreases the electron density of the carbonyl group to improve the reactivity (Figure 1, lower). Giacomelli et al. used this property to achieve the synthesis of ketones by nucleophilic substitution of *O*-DMT esters with Grignard/CuI reagents.[13] There is limited literature on the nucleophilic substitution of *N*-DMT amide, where DMT-NH_2 serves as a leaving group in the substitution with an aliphatic amine.[14] In this study, we evaluated the reactivity of an *N*-DMT amide for nucleophilic substitution by organometallic reagents comparing it with *N*-MMA amide (Weinreb amide). Moreover, unsymmetrical ketones were synthesized by sequential nucleophilic substitution with organometallic reagents on the carbonyl moiety of **1** flanked by MMA and DMT groups.

RESULTS AND DISCUSSION

Dual-activated urea **1** was readily prepared through a two-step reaction (Table 1). The addition of *N*-methoxy-*N*-methyl-

Table 1. Synthesis of Dual-Activated Ureas 1



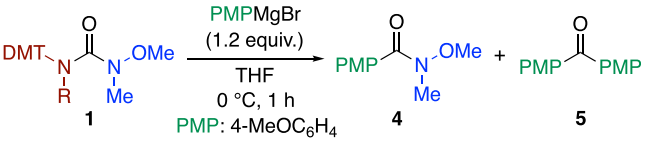
			yield (%)	
entry	R		3	1
1	Ph	a	quant.	quant.
2	4-MeC_6H_4	b	95	82
3	4-$MeOC_6H_4$	c	quant.	97
4	3-$MeOC_6H_4$	d	98	quant.
5	2-$MeOC_6H_4$	e	96	quant.
6	4-$F_3COC_6H_4$	f	94	quant.
7	4-ClC_6H_4	g	quant.	quant.
8	4-FC_6H_4	h	92	98
9	4-$F_3CC_6H_4$	i	quant.	84
10	4-$O_2NC_6H_4$	j	92	89[a]
11	Bu	k	quant.	32[b]
12	*c*-Hex	l	92	0[a,b,c]

[a]Under reflux. [b]LiN $(SiMe_3)_2$ was used as the base. [c]1,4-Dioxane was used as the solvent.

amine (NMA-H) hydrochloride to isocyanate **2** in pyridine furnished the corresponding ureas **3a**−**l** in excellent yields. The subsequent introduction of a DMT group to *N*-aryl ureas **3a**−**j** was efficiently achieved upon treatment with DMT-Cl in the presence of sodium hydride (entries 1−10), although reflux conditions were necessary for electron-poor urea **3h** (entry 10). In contrast, *N*-alkyl ureas **3k** and **3l** did not undergo *N*-modification under the same conditions. Using bulky lithium bis(trimethylsilyl)amide as a base was effective in this case to afford **1k** (entry 11); however, urea **1l** possessing a bulky cyclohexyl group was not obtained, even under heated conditions (entry 12).

The obtained dual-activated urea **1a** was subjected to a reaction with 4-methoxyphenylmagnesium bromide at 0 °C, which resulted in the formation of *N*-methoxy-*N*-(methyl)-anisamide **4**[15] in high yield (Table 2, entry 1). This indicates

Table 2. Substitution Reactions of Dual-Activated Ureas 1 by 4-$MeOC_6H_4MgBr$ (PMPMgBr)



	urea 1		yield (%)	
entry	R		4	5
1	Ph	a	82	17
2	4-MeC_6H_4	b	77	16
3	4-$MeOC_6H_4$	c	83	17
4	3-$MeOC_6H_4$	d	71	18
5	2-$MeOC_6H_4$	e	83	17
6	4-$F_3COC_6H_4$	f	71	25
7	4-ClC_6H_4	g	77	18
8	4-FC_6H_4	h	75	19
9	4-$F_3CC_6H_4$	i	71	13
10	4-$O_2NC_6H_4$	j	44	3
11	Bu	k	20	4

that DMT-NPh is a good leaving group. In this reaction, the second substitution afforded a small amount of symmetrical ketone **5**, but a byproduct, a tertiary alcohol, was not detected. The influence of the *N*-substituent on the reaction was investigated. *N*-Aryl ureas **1b**−**k** (entries 2−9) exhibited similar reactivities, furnishing **4** in high yields, but the reactivity of 4-nitrophenyl derivative **1j** was considerably lower (entry 10). On the other hand, *N*-butylurea **1k** was less reactive than *N*-aryl ureas, furnishing only a small amount of **4** under the same conditions (entry 11). Among the ureas tested, the most readily available *N*-phenylurea **1a** was employed as the substrate in subsequent studies.

To obtain insights into the different reactivities between *N*-aryl- and *N*-alkyl ureas, density functional theory (DFT) calculations for **1a** and **1k** were performed.[16] As shown in Figure 2, the DMT ring is coplanar with the urea moiety in the case of *N*-butylurea **1k**. In contrast, the DMT ring is not in the same plane as the carbonyl group because of steric repulsion with the phenyl group in the case of *N*-phenylurea **1a**. This distortion suppressed the electron-donating resonance effect of

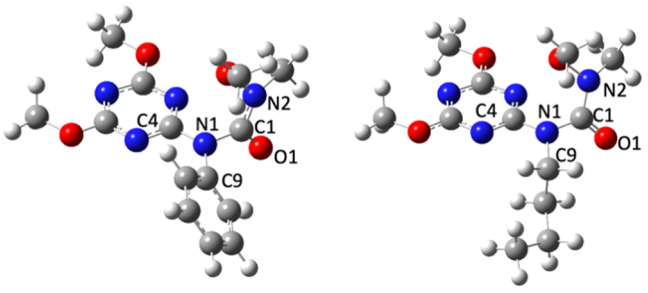
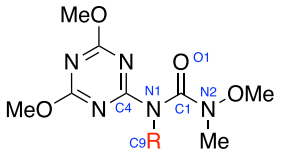


Figure 2. Optimized structures of **1a** and **1k**.

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483

the DMT-NPh group.[17] The least unoccupied molecular orbital (LUMO) level of **1a** was slightly lower than that of **1k**. This difference was confirmed by comparing bond lengths (Table 3). The N1−C1 bond length of **1a** is longer than that of **1k**, which decreases the double bond property of the N1−C1 bond and increases the reactivity of the DMT-N-Ph group as a leaving group. These structural features indicate that *N*-aryl urea is more reactive than *N*-alkyl urea and that the DMT-NH group is readily substituted compared to the MMA group.

Table 3. Selected Bond Angles (°) and Bond Lengths (Å) for the Calculated Structure



	R			R	
bond angle	Ph	Bu	bond length	Ph	Bu
C4−N1−C1−O1	105.2	122.2	N2−C1	1.377	1.383
C4−N1−C9	124.6	120.1	C1−O1	1.215	1.220
C4−N1−C1	116.6	120.0	N1−C1	1.449	1.423
C1−N1−C9	118.3	116.9	C4−N1	1.375	1.378

Dual-activated urea **1a** was subjected to reactions with other nucleophiles (Table 4). When urea **1a** was reacted with an equimolar Grignard reagent, substitution of the DMT-NPh group predominantly proceeded to afford the Weinreb amide in 82% yield (entry 1). Using an excessive amount of the Grignard reagent was effective, increasing the yield by up to 82%, although double substitution also occurred (entry 2). When excess amounts of the nucleophile were used at room temperature, symmetrical ketone **5** was exclusively obtained without any detectable formation of a tertiary alcohol (entry 3). When the Reformatsky reagent was used instead of the Grignard reagent, no reaction was observed (entry 4). No change was observed, even when PMPMgBr was added to this reaction mixture, presumably because of the inactivation of urea by tight coordination with the zinc species. In contrast, organolithium reagents yielded symmetrical ketones **5**, **9**, and **11**, with the recovery of urea **1a** even at −78 °C; however, a tertiary alcohol was not detected (entries 5−7). Hence, the DMT group effectively chelates magnesium ions, whereas the MMA group chelates either lithium or magnesium ions.

The different chelating abilities of the DMT and MMA groups prompted us to synthesize asymmetrical ketones in one pot (Table 5). First, two types of Grignard reagents were successively added to a solution of urea **1a** in tetrahydrofuran (THF). In the case of aromatic Grignard reagents, sequential substitution efficiently afforded unsymmetrical benzophenone derivatives **12**−**15** in moderate to high yields (entries 1−4). While butylmagnesium chloride furnished ketone **16** in good yield, bulkier aliphatic Grignard reagents exhibited lower reactivity (entries 5−7). In these reactions, symmetrical ketone and Weinreb amide were only obtained as byproducts without detectable tertiary alcohol. Less reactive ethynylmagnesium bromide could not consume the intermediately formed Weinreb amide under the employed conditions (entry 8).

A variety of organolithium reagents were employed as second nucleophiles (entries 9−15). Alkyllithium was substituted to afford the corresponding aryl alkyl ketones in moderate yields (entries 9 and 10). This protocol facilitated the synthesis of functionalized ketones by altering the lithium reagents (Figure 3). Pyridyl ketone **21** and ynone **22** were obtained in moderate yields (entries 11 and 12, respectively). Anionic dithiane and enolate were used as nucleophiles, which are synthetic equivalents of carbonyl functions, leading to **23** and **24**, respectively (entries 13 and 14). Moreover, lithiophosphonate also served as a nucleophile to afford functionalized phosphonate **25** (entry 15) in good yield.

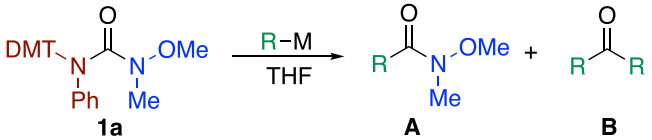
CONCLUSIONS

In summary, a DMT-amino group was found to activate the carbonyl group and prevent overaddition. This feature of the DMT-amino group is similar to that of the MMA group in Weinreb amides, but its reactivity is higher. Urea **1**, possessing a DMT-amino and an MMA group, served as a synthetic equivalent of the dicationic carbonyl group. Indeed, urea **1** underwent sequential nucleophilic substitution with different organometallic reagents to afford unsymmetrical ketones without any detectable tertiary alcohols. This protocol is a useful tool for elaborate syntheses.

EXPERIMENTAL SECTION

General. All reagents were purchased from commercial sources and used without further purification. Dry THF was

Table 4. Synthesis of Weinreb Amides and Symmetrical Ketones[a]



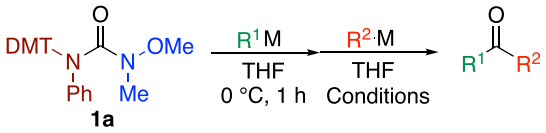
1a A B

			yield of product (%)			
entry	R-M (equiv.)	conditions	A		B	
1	PMPMgBr (1.0)	0 °C, 1 h	4	82	5	13
2	PMPMgBr (1.2)	0 °C, 1 h	4	82	5	17
3	PMPMgBr (4.0)	rt, 3 h	4	0	5	93
4	PhZnBr (1.2)	0 °C, 1 h	6	0	7	0
5	PMPLi (1.05)	−78 °C, 2 h then rt, 1 h	4	2	5	30
6	PhC≡CLi (1.1)	−78 °C, 1 h then 0 °C, 1 h	8	0	9	49
7	BuLi (1.2)	−78 °C, 10 min	10	0	11	41

[a]PMP: 4-MeOC$_6$H$_4$.

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483

Table 5. Synthesis of Unsymmetrical Ketones by Sequential Substitution[a]



entry	R^1M (equiv.)	R^2M (equiv.)	conditions	product	yield (%)
1	PMPMgBr (1.2)	PhMgBr (1.4)	0 °C then rt, 15 h	**12**	82
2	3-$MeOC_6H_4MgBr$ (1.2)	PhMgBr (1.4)	0 °C then rt, 15 h	**13**	54
3	2-$MeOC_6H_4MgBr$ (1.2)	PhMgBr (1.4)	0 °C then rt, 15 h	**14**	53
4	4-FC_6H_4MgBr (1.2)	PMPMgBr (1.4)	0 °C then rt, 15 h	**15**	70
5	BuMgCl (1.2)[b]	PMPMgBr (1.4)	−78 °C, 1 h then rt, 17 h	**16**	68
6	*i*-BuMgCl (1.2)[b]	PMPMgBr (1.4)	−78 °C, 1 h then rt, 17 h	**17**	22
7	*c*-HexMgCl (1.2)	PMPMgBr (1.4)	0 °C then rt, 15 h	**18**	30
8	PMPMgBr (1.2)	HC≡CMgBr (1.4)	0 °C then rt, 19 h	**19**	34
9	PMPMgBr (1.2)	BuLi (1.0)	−78 °C, 1 h then 0 °C, 10 min	**16**	64
10	PMPMgBr (1.2)	*sec*-BuLi (1.4)	0 °C then rt, 19 h	**20**	46
11	PMPMgBr (1.2)	PyLi (1.2)	−78 °C, 1 h then rt, 20 h	**21**	59
12	PMPMgBr (1.2)	PhC≡CLi (1.4)	0 °C then rt, 19 h	**22**	58
13	PMPMgBr (1.2)	PhDT-Li (1.3)	−78 °C, 1 h then 0 °C, 30 min	**23**	35
14	PMPMgBr (1.2)	BuOE-OLi (2.0)	−78 °C, 2 h	**24**	73
15	PMPMgBr (1.2)	$(MeO)_2POCH_2Li$ (2.3)	−78 °C, 1 h then 0 °C, 1 h	**25**	76

[a]PMP: 4-$MeOC_6H_4$, Py: 2-pyridyl, PhDT: 2-phenyl-1,3-dithiane-2-yl, BuOE: 1-*tert*-butoxy-1-ethenyl. [b]The first substitution was conducted at −78 °C for 1 h.

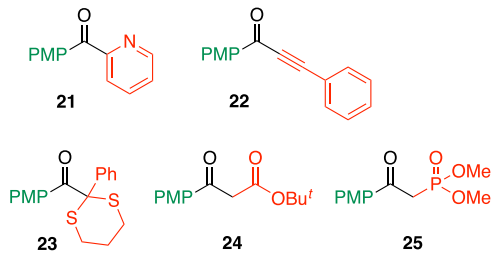


Figure 3. Functionalized ketones **21**−**25**.

also purchased from a commercial source and used as received. Gravity column chromatography was performed using Kanto Chemical Co. spherical silica gel 60N with a particle size of 63−210 μm. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AVANCE III 400 spectrometer (400 MHz, 100 MHz, and 376 MHz, respectively). All chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hz. The ^{1}H and ^{13}C NMR chemical shifts are relative to tetramethylsilane; the resonance of the residual protons of chloroform was used as an internal standard for ^{1}H (δ 7.26 ppm) and all-d solvent peaks for ^{13}C (δ 77.0 ppm).[18] The assignments of the ^{13}C NMR were performed by DEPT experiments. ^{19}F NMR chemical shifts are relative to hexafluorobenzene in $CDCl_3$ at δ = -163.0 ppm (external reference).[19] High-resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. Melting points were recorded on an Anatec Yanaco MP-J3 and were uncorrected. Geometrical optimization was carried out at the B3LYP/6-31g(d,p) level of theory implemented on the Gaussian 09 package.[16]

Preparation of Dual-Activated Urea 1. *Amination of Isocyanate 2. N-Methoxy-N-methyl-N′-phenylurea (**3a**).* To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.74 g, 7.5 mmol) in pyridine (5.0 mL), phenyl isocyanate (**2a**, 0.54 mL, 5.0 mmol) was added dropwise at 0 °C, and the resulting mixture was warmed up to room temperature. After stirring for 1 day, the reaction was quenched with 10% aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford *N*-methoxy-*N*-methyl-*N′*-phenylurea (**3a**) (0.90 g, 5.0 mmol, quant.) as a white solid. An analytically pure sample was obtained by recrystallization from CH_2Cl_2/hexane (1:4). Mp 61.0−62.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.75 (s, 3H), 7.06 (tt, J = 0.8, 7.6 Hz, 1H), 7.26−7.34 (m, 2H), 7.43−7.49 (m, 2H), 7.72 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9 (CH_3), 61.6 (CH_3), 119.3 (CH), 123.4 (CH), 128.9 (CH), 137.9 (C), 157.2 (C); HRMS (EI) m/z [M^+] calcd. for $C_9H_{12}N_2O_2$: 180.0899; found: 180.0895.

*Other Ureas **3** Were Synthesized in the Same Way. N-Methoxy-N-methyl-N′-(4-methylphenyl)urea (**3b**).* White solid. Mp 95.5−96.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.17 (s, 3H), 3.75 (s, 3H), 7.11 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH_3), 35.0 (CH_3), 61.6 (CH_3), 119.5 (CH), 129.4 (CH), 133.0 (C), 135.3 (C), 157.4 (C); HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{14}N_2O_2$: 194.1055; found: 194.1057.

*N-Methoxy-N-methyl-N′-(4-methoxyphenyl)urea (**3c**).* Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 6.85 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 55.4 (CH_3), 61.6 (CH_3), 114.1 (CH), 121.4 (CH), 130.9 (C), 156.0 (C), 157.7 (C); HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{14}N_2O_3$: 210.1004; found: 210.1003.

*N-Methoxy-N-methyl-N′-(3-methoxyphenyl)urea (**3d**).* Pale yellow solid. Mp 88.5−90.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 6.60−6.65 (m, 1H), 6.90−6.95 (m, 1H), 7.16−7.22 (m, 1H), 7.23−7.25 (m, 1H), 7.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9 (CH_3), 55.2 (CH_3), 61.6 (CH_3), 104.8 (CH), 109.5 (CH), 111.5 (CH), 129.6 (CH), 139.2 (C), 157.1 (C), 160.2 (C);

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483

HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{14}N_2O_3$: 210.1004; found: 210.1004.

*N-Methoxy-N-methyl-N′-(2-methoxyphenyl)urea (**3e**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 6.86 (dd, J = 2.0, 7.6 Hz, 1H), 6.92−7.02 (m, 2H), 8.21 (dd, J = 2.0, 7.6 Hz, 1H), 8.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9 (CH_3), 55.7 (CH_3), 61.5 (CH_3), 109.8 (CH), 118.6 (CH), 121.0 (CH), 122.6 (CH), 127.7 (C), 147.9 (C), 157.1 (C); HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{14}N_2O_3$: 210.1004; found: 210.1001.

*N-Methoxy-N-methyl-N′-[4-(trifluoromethoxy)phenyl]-urea (**3f**).* White solid. Mp 73.5−74.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.77 (s, 3H), 7.16 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8 (CH_3), 61.7 (CH_3), 120.4 (CH), 120.5 (q, J = 255.1 Hz, CF_3), 121.7 (CH), 136.7 (C), 144.8 (d, J = 1.6 Hz, C), 157.1 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.4; HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{11}F_3N_2O_3$: 264.0722; found: 264.0724.

*N-Methoxy-N-methyl-N′-(4-chlorophenyl)urea (**3g**).* White solid. Mp 77.0−77.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.76 (s, 3H), 7.26 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8 (CH_3), 61.7 (CH_3), 120.6 (CH), 128.4 (C), 128.9 (CH), 136.6 (C), 157.0 (C); HRMS (EI) m/z [M^+] calcd. for $C_9H_{11}ClN_2O_2$: 214.0509; found: 214.0509.

*N-Methoxy-N-methyl-N′-(4-fluorophenyl)urea (**3h**).* White solid. Mp 71.5−72.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 3H), 3.76 (s, 3H), 7.00 (dd, J = 8.8, 8.8 Hz, 2H), 7.41 (dd, J = 4.8, 8.8 Hz, 2H), 7.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9 (CH_3), 61.6 (CH_3), 115.5 (d, J = 22.2 Hz, CH), 121.2 (d, J = 7.9 Hz, CH), 133.9 (d, J = 2.6 Hz, C), 157.3 (C), 159.0 (d, J = 240.8 Hz, C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.82 to −120.73; HRMS (EI) m/z [M^+] calcd. for $C_9H_{11}FN_2O_2$: 198.0805; found: 198.0802.

*N-Methoxy-N-methyl-N′-[4-(trifluoromethyl)phenyl]urea (**3i**).* White solid. Mp 91.0−92.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (s, 3H), 3.78 (s, 3H), 7.56 (d, J = 9.2 Hz, 2H), 7.59 (d, J = 9.2 Hz, 2H), 7.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.6 (CH_3), 61.7 (CH_3), 118.7 (CH), 124.2 (q, J = 269.7 Hz, CF_3), 125.1 (q, J = 32.6 Hz, C), 126.2 (q, J = 3.7 Hz, CH), 141.2 (C), 156.6 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.3; HRMS (EI) m/z [M^+] calcd. for $C_{10}H_{11}F_3N_2O_2$: 248.0773; found: 248.0773.

*N-Methoxy-N-methyl-N′-(4-nitrophenyl)urea (**3j**).* Yellow solid. Mp 147.0−148.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 3H), 3.83 (s, 3H), 7.67 (d, J = 9.2 Hz, 2H), 8.05 (br s, 1H), 8.22 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4 (CH_3), 61.8 (CH_3), 118.3 (CH), 125.1 (CH), 142.9 (C), 144.1 (C), 156.0 (C); HRMS (EI) m/z [M^+] calcd. for $C_9H_{11}N_3O_4$: 225.0750; found: 225.0749.

*N-Methoxy-N-methyl-N′-butylurea (**3k**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.29−1.42 (m, 2H), 1.46−1.56 (m, 2H), 3.08 (s, 3H), 3.19−3.27 (m, 2H), 3.66 (s, 3H), 5.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 19.9 (CH_2), 32.1 (CH_2), 35.5 (CH_3), 39.6 (CH_2), 61.2 (CH_3), 160.4 (C); HRMS (EI) m/z [M^+] calcd. for $C_7H_{16}N_2O_2$: 160.1212; found: 160.1212.

*N-Methoxy-N-methyl-N′-cyclohexylurea (**3l**).* White solid. Mp 89.5−90.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.23 (m, 3H), 1.30−1.44 (m, 2H), 1.57−1.66 (m, 1H), 1.66−1.76 (m, 2H), 1.89−1.98 (m, 2H), 3.08 (s, 3H), 3.55−3.67 (m, 1H), 3.65 (s, 3H), 5.66 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (CH_2), 25.5 (CH_2), 33.6 (CH_2), 35.6 (CH_3), 48.6 (CH), 61.2 (CH_3), 159.6 (C); HRMS (EI) m/z [M^+] calcd. for $C_9H_{18}N_2O_2$: 186.1368; found: 186.1368.

*N-Triazinylation of **3**. N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-phenylurea (**3a**).* To a solution of urea **3a** (0.18 g, 1.0 mmol) in THF (4.0 mL) was added portionwise NaH (60% dispersion in mineral oil, 0.16 g, 4.0 mmol) at 0 °C, and the resulting mixture was allowed to warm up to room temperature. After stirring for 30 min, 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.25 g, 1.4 mmol) was added, and the mixture was stirred at room temperature for another 1 day. The reaction was quenched with 10% aqueous NH_4Cl and extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure to give a white solid as a residue. Further purification was performed by column chromatography on silica gel to afford *N*-methoxy-*N′*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*-methyl-*N′*-phenylurea (**1a**) (eluted with hexane/ethyl acetate = 2/1, 0.32 g, 1.0 mmol, quant.) as a white solid. Mp 63.5−64.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.65 (s, 3H), 3.93 (s, 6H), 7.26−7.33 (m, 1H), 7.37−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 54.9 (CH_3), 61.3 (CH_3), 126.1 (CH), 127.1 (CH), 129.1 (CH), 137.7 (C), 154.8 (C), 167.3 (C), 172.5 (C); HRMS (EI) m/z [M^+] calcd. for $C_{14}H_{17}N_5O_4$: 319.1281; found: 319.1280.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(4-methylphenyl)urea (**1b**).* White solid. Mp 95.0−96.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.32 (s, 3H), 3.66 (s, 3H), 3.92 (s, 6H), 7.15 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 35.1 (CH_3), 54.9 (CH_3), 61.3 (CH_3), 126.0 (CH), 129.7 (CH), 135.0 (C), 137.1 (C), 154.9 (C), 167.3 (C), 172.4 (C); HRMS (EI) m/z [M^+] calcd. for $C_{15}H_{19}N_5O_4$: 333.1437; found: 333.1437.

*N-methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(4-methoxyphenyl)urea (**1c**).* White solid. Mp 92.5−93.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 3.92 (s, 6H), 6.92 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 54.9 (CH_3), 55.4 (CH_3), 61.3 (CH_3), 114.3 (CH), 127.9 (CH), 130.4 (C), 154.9 (C), 158.6 (C), 167.5 (C), 172.4 (C); HRMS (EI) m/z [M^+] calcd. for $C_{15}H_{19}N_5O_5$: 349.1386; found: 349.1385.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(3-methoxyphenyl)urea (**1d**).* Light brown solid. Mp 68.0−69.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 3.93 (s, 6H), 6.82−6.86 (m, 1H), 6.97−7.02 (m, 2H), 7.27−7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2 (CH_3), 54.9 (CH_3), 55.3 (CH_3), 61.3 (CH_3), 111.9 (CH), 112.8 (CH), 118.4 (CH), 129.6 (CH), 138.7 (C), 154.7 (C), 160.0 (C), 167.2 (C), 172.5 (C); HRMS (EI) m/z [M^+] calcd. for $C_{15}H_{19}N_5O_5$: 349.1386; found: 349.1386.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(2-methoxyphenyl)urea (**1e**).* Light brown solid. Mp 103.0−104.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.68 (s, 3H), 3.79 (s, 3H), 3.90 (s, 6H), 6.94−7.01 (m, 2H), 7.27−7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2 (CH_3), 54.8 (CH_3), 55.6 (CH_3), 60.9 (CH_3), 112.0 (CH), 120.9 (CH), 127.3 (C), 128.5 (CH), 129.1 (CH), 154.8 (C), 155.0 (C), 168.0 (C), 172.5 (C); HRMS (EI) m/z [M^+] calcd. for $C_{15}H_{19}N_5O_5$: 349.1386; found: 349.1385.

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-[4-(trifluoromethoxy)phenyl]urea (**1f**).* White solid. Mp 105.0−106.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.67 (s, 3H), 3.94 (s, 6H), 7.22−7.28 (m, 2H), 7.46 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 55.0 (CH_3), 61.5 (CH_3), 120.4 (q, J = 256.3 Hz, CF_3), 121.5 (CH), 127.7 (CH), 136.2 (C), 147.7 (C), 154.6 (C), 167.2 (C), 172.5 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.1; HRMS (EI) m/z [M$^+$] calcd. for $C_{15}H_{16}F_3N_5O_5$: 403.1104; found: 403.1103.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(4-chlorophenyl)urea (**1g**).* White solid. Mp 108.5−109.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.66 (s, 3H), 3.94 (s, 6H), 7.33−7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 55.0 (CH_3), 61.4 (CH_3), 127.5 (CH), 129.2 (CH), 132.8 (C), 136.3 (C), 154.5 (C), 167.2 (C), 172.5 (C); HRMS (EI) m/z [M$^+$] calcd. for $C_{14}H_{16}ClN_5O_4$: 353.0891; found: 353.0890.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(4-fluorophenyl)urea (**1h**).* Pale yellow solid. Mp 71.5−72.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.67 (s, 3H), 3.93 (s, 6H), 7.06−7.13 (m, 2H), 7.35−7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0 (CH_3), 54.9 (CH_3), 61.4 (CH_3), 116.0 (d, J = 22.6 Hz, CH), 128.4 (d, J = 8.4 Hz, CH), 133.7 (d, J = 3.1 Hz, C), 154.7 (C), 161.5 (d, J = 246.0 Hz, C), 167.4 (C), 172.4 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.47 to −115.36; HRMS (EI) m/z [M$^+$] calcd. for $C_{14}H_{16}FN_5O_4$: 337.1186; found: 337.1186.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-[4-(trifluoromethyl)phenyl]urea (**1i**).* White solid. Mp 102.5−103.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.66 (s, 3H), 3.96 (s, 6H), 7.54 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 55.1 (CH_3), 61.5 (CH_3), 123.8 (q, J = 270.3 Hz, CF_3), 125.7 (CH), 126.2 (q, J = 3.6 Hz, CH), 128.7 (q, J = 32.6 Hz, C), 141.0 (C), 154.4 (C), 167.0 (C), 172.5 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.8; HRMS (EI) m/z [M$^+$] calcd. for $C_{15}H_{16}F_3N_5O_4$: 387.1154; found: 387.1153.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-(4-nitrophenyl)urea (**1j**).* Pale yellow solid. Mp 120.0−120.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.66 (s, 3H), 3.98 (s, 6H), 7.61 (d, J = 9.2 Hz, 2H), 8.27 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1 (CH_3), 55.2 (CH_3), 61.7 (CH_3), 124.6 (CH), 125.1 (CH), 143.7 (C), 145.4 (C), 154.1 (C), 166.8 (C), 172.5 (C); HRMS (EI) m/z [M$^+$] calcd. for $C_{14}H_{16}N_6O_6$: 364.1131; found: 364.1131.

*N-Methoxy-N-methyl-N′-(4,6-dimethoxyl-1,3,5-triazin-2-yl)-N′-butylurea (**1k**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.31−1.43 (m, 2H), 1.62−1.72 (m, 2H), 3.28 (s, 3H), 3.67 (s, 3H), 3.78−3.84 (m, 2H), 3.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 20.1 (CH_2), 30.6 (CH_2), 35.2 (CH_3), 46.4 (CH_2), 54.8 (CH_3), 61.2 (CH_3), 156.1 (C), 167.3 (C), 172.3 (C); HRMS (EI) m/z [M$^+$] calcd. for $C_{12}H_{21}N_5O_4$: 299.1594; found: 299.1592.

*Reaction of Urea **1** with Organometallic Reagent.* To a solution of **1a** (R = Ph, 96 mg, 0.30 mmol) in dry THF (1.5 mL), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 0.72 mL, 0.36 mmol) was added dropwise at 0 °C under an argon atmosphere, and the resulting mixture was stirred at the same temperature for 1 h. After quenching the reaction with 10% aqueous NH_4Cl, the mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure to afford a white solid as a residue. Yields of Weinreb amide **4a** and symmetrical ketone **5a** were determined by a comparison of integral values with those of 1,1,2,2-tetrachloroethane as an internal standard in the ^{1}H NMR of the crude mixture.[15]

When other ureas, organometallic reagents, and other reaction conditions were used, experiments were conducted in the same way. Each product could be isolated by column chromatography on silica gel using hexane/ethyl acetate (3/1 to 2/1) as an eluent. All of the products are known compounds and their structures were confirmed by the comparison of the ^{1}H NMR spectrum with that of authentic samples.[20]

*Sequential Substitution of Urea **1** with Organometallic Reagents.* To a solution of **1a** (54.6 mg, 0.171 mmol) in dry THF (2.0 mL), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 0.42 mL, 0.210 mmol) was added dropwise under an argon atmosphere at 0 °C, and the resulting mixture was stirred at the same temperature for another 1 h. Then, phenylmagnesium bromide (1.0 M in THF, 0.24 mL, 0.240 mmol) was added dropwise at 0 °C. After gradually warming up to room temperature, the mixture was stirred for 15 h. The reaction was quenched with 10% aqueous NH_4Cl and extracted with ethyl acetate (20 mL × 2). The combined organic layer was washed with brine (20 mL × 1), dried over Na_2SO_4, and concentrated under reduced pressure to afford a white solid as a residue. Each product could be isolated by column chromatography on silica gel using hexane/ethyl acetate (3/1 to 2/1) as an eluent. Structures of the products, Weinreb amide and ketone, were confirmed by a comparison of the ^{1}H NMR spectrum with that of authentic samples.[5] Yields of Weinreb amide **4a** and symmetrical ketone **5a** were determined by a comparison of integral values with those of 1,1,2,2-tetrachloroethane as an internal standard in the ^{1}H NMR using $CDCl_3$ as a solvent.

When other ureas, organometallic reagents, and other reaction conditions were used, experiments were conducted in the same way. Each product could be isolated by column chromatography on silica gel using hexane/ethyl acetate (3/1 to 2/1) as an eluent. All of the products are known compounds and the structures were confirmed by a comparison of the ^{1}H NMR spectrum with that of authentic samples.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06756.

Experimental procedures, characterization of compounds, and NMR spectral data of urea **1** and **3** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Shotaro Hirao − *Faculty of Science and Technology, Oita University, Oita 870-1192, Japan;* orcid.org/0000-0001-6759-4059; Phone: +81-97-554-7959; Email: hirao-shoutarou@oita-u.ac.jp

Authors

Rumi Saeki − *Graduate School of Engineering, Oita University, Oita 870-1192, Japan*

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483

Toru Takahashi − *Faculty of Science and Technology, Oita University, Oita 870-1192, Japan*
Kento Iwai − *School of Environmental Science and Engineering, Kochi University of Technology, Kochi 782-8502, Japan; Research Center for Molecular Design, Kochi University of Technology, Kochi 782-8502, Japan;* orcid.org/0000-0002-0923-604X
Nagatoshi Nishiwaki − *School of Environmental Science and Engineering, Kochi University of Technology, Kochi 782-8502, Japan; Research Center for Molecular Design, Kochi University of Technology, Kochi 782-8502, Japan;* orcid.org/0000-0002-6052-8697
Yasushi Ohga − *Faculty of Science and Technology, Oita University, Oita 870-1192, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c06756

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Office for Research Initiative and Development of Nagasaki University for analysis support.

■ REFERENCES

(1) Recent papers: (a) Liang, J.; Wang, G.; Dong, L.; Pang, X.; Qin, J.; Xu, X.; Shao, X.; Li, Z. CF_2DSO_2Na: An Effective Precursor Reagent for Deuteriodifluoromethylthiolation and Deuteriodifluoromethylation. *Org. Lett.* **2021**, *23*, 5545−5548. (b) He, Q.; Ye, J.-L.; Xu, F.-F.; Geng, H.; Chen, T.-T.; Chen, H.; Huang, P.-Q. Tf_2O/TTBP (2,4,6-Tri-tert-butylpyrimidine): An Alternative Amide Activation System for the Direct Transformations of Both Tertiary and Secondary Amides. *J. Org. Chem.* **2021**, *86*, 16300−16314. (c) Arribas, A.; Calvelo, M.; Fernandez, D. F.; Rodrigues, C. A. B.; Mascarenas, J. L.; Lopez, F. Highly Enantioselective Iridium(I)-Catalyzed Hydrocarbonation of Alkenes: A Versatile Approach to Heterocyclic Systems Bearing Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2021**, *60*, 19297−19305. (d) Furukawa, H.; Miyamoto, Y.; Hirata, Y.; Watanabe, K.; Hitomi, Y.; Yoshitomi, Y.; Aida, J.; Noguchi, N.; Takakura, N.; Takami, K.; Miwatashi, S.; Hirozane, Y.; Hamada, T.; Ito, R.; Ookawara, M.; Moritoh, Y.; Watanabe, M.; Maekawa, T. Design and Identification of a GPR40 Full Agonist (SCO-267) Possessing a 2-Carbamoylphenyl Piperidine Moiety. *J. Med. Chem.* **2020**, *63*, 10352−10379. (e) Heinz, B.; Djukanovic, D.; Ganiek, M. A.; Martin, B.; Schenkel, B.; Knochel, P. Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow. *Org. Lett.* **2020**, *22*, 493−496. (f) Guo, S.; Sun, L.; Li, X.; Zhang, X.; Fan, X. Selective Synthesis of Indazolo [2,3-*a*]quinolines via Rh(III)-Catalyzed Oxidant-Free [4+2] or [5+1] Annulation of 2- Aryl-2H-indazoles with α-Diazo Carbonyl Compounds. *Adv. Synth. Catal.* **2020**, *362*, 913−926. (g) Peňaška, T.; Mojzes, M. M.; Filo, J.; Jurdakova, H.; Meciarova, M.; Sebesta, R. Organocatalysts Effect on the Stereoselectivity of [2,3]-Wittig Rearrangement. *Eur. J. Org. Chem.* **2019**, *2019*, 605−610. (h) Mears, P. R.; Hoekman, S.; Rye, C. E.; Bailey, F. P.; Byrne, D. P.; Eyers, P. A.; Thomas, E. J. Towards 20,20-Difluorinated Bryostatin: Synthesis and Biological Evaluation of C17, C27-Fragments. *Org. Biomol. Chem.* **2019**, *17*, 1487−1505. (i) Gil, A.; Lamariano-Merketegi, J.; Lorente, A.; Albericio, F.; Alvarez, M. Synthesis of (*E*)-4-Bromo-3-methoxybut-3-en-2-one, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A-C. *Chem. - Eur. J.* **2016**, *22*, 7033−7035.

(2) (a) Chen, T.; Lee, S. W.; Abelt, C. J. 1,5-Prodan Emits from a Planar Intramolecular Charge-Transfer Excited State. *ACS Omega* **2018**, *3*, 4816−4823. (b) Kondoh, A.; Aoki, T.; Terada, M. Generation and Application of Homoenolate Equivalents Utilizing [1,2]-Phospha-Brook Rearrangement under Brønsted Base Catalysis. *Chem. - Eur. J.* **2017**, *23*, 2769−2773. (c) Suo, J.-J.; Du, J.; Liu, Q.-R.; Chen, D.; Ding, C.-H.; Peng, Q.; Hou, X.-L. Highly Diastereo- and Enantioselective Palladium-Catalyzed [3 + 2] Cycloaddition of Vinyl Epoxides and α, β-Unsaturated Ketones. *Org. Lett.* **2017**, *19*, 6658−6661. (d) Evans, D. A.; Borg, G.; Scheidt, K. A. Remarkably Stable Tetrahedral Intermediates: Carbinols from Nucleophilic Additions to *N*-Acylpyrroles. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188−3191.

(3) Recent papers: (a) Pudner, G. L.; Camp, I.; Scheerer, J. R. A Nonoxidative Sequence for the Preparation of 1,2-Diketone Derivatives Using Aldehyde and Organometallic Building Blocks. *J. Org. Chem.* **2022**, *87*, 8213−8222. (b) Zhou, X.; Yu, T.; Dong, G. Site-Specific and Degree-Controlled Alkyl Deuteration via Cu-Catalyzed Redox-Neutral Deacylation. *J. Am. Chem. Soc.* **2022**, *144*, 9570−9575. (c) Komatsuda, M.; Ohki, H.; Kondo, H., Jr; Suto, A.; Yamaguchi, J. Ring-Opening Fluorination of Isoxazoles. *Org. Lett.* **2022**, *24*, 3270−3274. (d) Guo, R.; Chang, Y.-C.; Herter, L.; Salome, C.; Braley, S. E.; Fessard, T. C.; Brown, M. K. *J. Am. Chem. Soc.* **2022**, *144*, 7988−7994.

(4) Recent papers: (a) Zhang, H.-X.; Guo, R.-L.; Zhang, X.-L.; Wang, M.-Y.; Zhao, B.-Y.; Gao, Y.-R.; Jia, Q.; Wang, Y.-Q. Synthesis of Acyl Hydrazides via a Radical Chemistry of Azocarboxylic tert-Butyl Esters. *J. Org. Chem.* **2022**, *87*, 6573−6587. (b) Wang, Z.; Xu, G.; Lu, H.; Wu, S.; Liao, S.; Hu, Y.; Lin, J.; Liu, Z. An Alternative Process for the Synthesis of the Key Intermediate of Ritlecitinib. *Tetrahedron* **2021**, *101*, No. 132503. (c) Gallagher-Duval, S.; Lapointe, V.; Belanger, G. Functionalized Polyhydroquinolines from Amino Acids Using a Key One-Pot Cyclization Cascade and Application to the Synthesis of (±)-Δ^7-Mesembrenone. *Org. Lett.* **2021**, *23*, 8606−8611.

(5) Takeda, N.; Kobori, Y.; Yasui, M.; Matsumoto, Y.; Orihara, K.; Kido, Y.; Ueda, M. Sequential Nucleophilic Addition/1,2-Rearrangement of *N*-Iminolactam: A Ring-Contractive Strategy for the Synthesis of 2-Acyl Pyrrolidines. *Tetrahedron Lett.* **2021**, *73*, No. 153098.

(6) Recent papers: (a) Chen, P.-F.; Zhou, B.; Wu, P.; Wang, B.; Ye, L.-W. Bronsted Acid Catalyzed Dearomatization by Intramolecular Hydroalkoxylation/Claisen Rearrangement: Diastereo- and Enantioselective Synthesis of Spirolactams. *Angew. Chem., Int. Ed.* **2021**, *60*, 27164−27170. (b) Hu, X.-Q.; Liu, Z.-K.; Hou, Y.-X.; Xu, J.-H.; Gao, Y.; Merging, C.-H. Activation and Strain-Release in Ruthenium-Catalyzed Isoindolinone Synthesis. *Org. Lett.* **2021**, *23*, 6332−6336. (c) Asahara, H.; Arikiyo, K.; Nishiwaki, N. Development of Variously Functionalized Nitrile Oxides. *Beilstein J. Org. Chem.* **2015**, *11*, 1241−1245.

(7) (a) Ishihara, K.; Nishimura, K.; Yamakawa, K. Enantio- and Site-Selective α-Fluorination of *N*-Acyl 3,5-Dimethylpyrazoles Catalyzed by Chiral π-Cu Complexes. *Angew. Chem., Int. Ed.* **2020**, *59*, 17641−17647. (b) Kuang, Y.; Wang, K.; Shi, X.; Huang, X.; Meggers, E.; Wu, J. Asymmetric Synthesis of 1,4-Dicarbonyl Compounds from Aldehydes by Hydrogen Atom Transfer Photocatalysis and Chiral Lewis Acid Catalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 16859−16863. (c) Ding, X.; Tian, C.; Hu, Y.; Gong, L.; Meggers, E. Tuning the Basicity of a Metal-Templated Bronsted Base to Facilitate the Enantioselective Sulfa-Michael Addition of Aliphatic Thiols to α,β-Unsaturated N-Acylpyrazoles. *Eur. J. Org. Chem.* **2016**, *2016*, 887−890.

(8) Heller, S. T.; Newton, J. N.; Fu, T.; Sarpong, R. One-pot Unsymmetrical Ketone Synthesis Employing a Pyrrole-Bearing Formal Carbonyl Dication Linchpin Reagent. *Angew. Chem., Int. Ed.* **2015**, *54*, 9839−9843.

(9) Recent papers dealing with synthetic methods for unsymmetrical ketones: (a) Tien, C.-H.; Trofimova, A.; Holownia, A.; Kwak, B. S.; Larson, R. T.; Yudin, A. K. Carboxyboronate as a Versatile in situ CO Surrogate in Palladium-Catalyzed Carbonylative Transformations. *Angew. Chem., Int. Ed.* **2021**, *60*, 4342−4349. (b) Djukanovic, D.; Heinz, B.; Mandrelli, F.; Mostarda, S.; Filipponi, P.; Martin, B.; Knochel, P. Continuous Flow Acylation of (Hetero)aryllithiums with Polyfunctional *N*,*N*-Dimethylamides and Tetramethylurea in Toluene. *Chem. - Eur. J.* **2021**, *27*, 13977−13981. (c) Zoller, B.; Zapp, J.;

Huy, P. H. Rapid Organocatalytic Formation of Carbon Monoxide: Application towards Carbonylative Cross Couplings. *Chem. - Eur. J.* **2020**, *26*, 9632−9638. (d) Levesque, T. M.; Kinney, R. G.; Arndtsen, B. A. A Palladium-Catalyzed C−H Functionalization Route to Ketones *via* the Oxidative Coupling of Arenes with Carbon Monoxide. *Chem. Sci.* **2020**, *11*, 3104−3109. (e) Hurst, T. E.; Deichert, J. A.; Kapeniak, L.; Lee, R.; Harris, J.; Jessop, P. G.; Snieckus, V. Sodium Methyl Carbonate as an Effective C1 Synthon. Synthesis of Carboxylic Acids, Benzophenones, and Unsymmetrical Ketones. *Org. Lett.* **2019**, *21*, 3882−3885. (f) Wu, J.; Yang, X.; He, Z.; Mao, X.; Hatton, T. A.; Jamison, T. F. Continuous Flow Synthesis of Ketones from Carbon Dioxide and Organolithium or Grignard Reagents. *Angew. Chem., Int. Ed.* **2014**, *53*, 8416−8420.

(10) Whipple, W. L.; Reich, H. J. Use of *N,N′*-Dimethoxy-*N,N′*-dimethylurea as a Carbonyl Dication Equivalent in Organometallic Addition Reactions. Synthesis of Unsymmetrical Ketones. *J. Org. Chem.* **1991**, *56*, 2911−2912.

(11) Hlasta, D. J.; Court, J. J. Tandem Organometallic Addition Reactions to *N*-Methoxy-ureas and Urethanes in the Preparation of Unsymmetrical and Symmetrical Ketones. *Tetrahedron Lett.* **1989**, *30*, 1773−1776.

(12) Lee, N. R.; Lee, J. I. One-pot Synthesis of Ketones Using *N*-Methoxy-*N*-methyl-2-pyridyl Urethane. *Synth. Commun.* **1999**, *29*, 1249−1255.

(13) De Luca, L.; Giacomelli, G.; Porcheddu, A. A Simple Preparation of Ketones. *N*-Protected α-Amino Ketones from α-Amino Acids. *Org. Lett.* **2001**, *3*, 1519−1521.

(14) Silin, V. I.; Karlik, E. A.; Ridge, K. D.; Vanderah, D. J. Development of Surface-Based Assays for Transmembrane Proteins: Selective Immobilization of Functional CCR5, a G Protein-Coupled Receptor. *Anal. Biochem.* **2006**, *349*, 247−253.

(15) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. Palladium-Catalyzed Carbonylation Reactions of Aryl Bromides at Atmospheric Pressure: A General System Based on Xantphos. *J. Org. Chem.* **2008**, *73*, 7102−7107.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J.; et al. *Gaussian 09*, revision C.01; Gaussian, Inc.: Wallingford, CT, 2010.

(17) (a) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Reversible Twisting of Primary Amides via Ground State N−C(O) Destabilization: Highly Twisted Rotationally Inverted Acyclic Amides. *J. Am. Chem. Soc.* **2018**, *140*, 727−734. (b) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N−C/O−C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161−11172.

(18) Babij, N. R.; McCusker, E. O.; Whiteker, G. T.; Canturk, B.; Choy, N.; Creemer, L. C.; De Amicis, C. V.; Hewlett, N. M.; Johnson, P. L.; Knobelsdorf, J. A.; Li, F.; Lorsbach, B. A.; Nugent, B. M.; Ryan, S. J.; Smith, M. R.; Yang, Q. NMR Chemical Shifts of Trace Impurities: Industrially Preferred Solvents Used in Process and Green Chemistry. *Org. Process Res. Dev.* **2016**, *20*, 661−667.

(19) Lucassen, A. C. B.; Zubkov, T.; Shimon, L. J. W.; van der Boom, M. E. Design, synthesis and crystal structure of a multiple donor−acceptor halogen bonded stilbazole: assembly of unimolecular interconnected helices. *CrystEngComm* **2007**, *9*, 538−540.

(20) Compounds **5** and **11** are commercially available. **9** (a) Alfonzo, E.; Alfonso, F. S.; Beeler, A. B. Redesign of a Pyrylium Photoredox Catalyst and Its Application to the Generation of Carbonyl Ylides. *Org. Lett.* **2017**, *19*, 2989−2992. **12** (b) Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-Catalysed Suzuki−Miyaura Coupling of Amides. *Nat. Chem.* **2016**, *8*, 75−79. **13**: (c) Mai, S.; Li, W.; Li, X.; Zhao, Y.; Song, Q. Palladium-Catalyzed Suzuki−Miyaura Coupling of Thioureas or Thioamides. *Nat. Commun.* **2019**, *10*, No. 5709. 14: (d) Gooßen, L.; Rudolphi, F.; Oppel, C.; Rodriguez, N. Synthesis of Ketones from α-Oxocarboxylates and Aryl Bromides by Cu/Pd-Catalyzed Decarboxylative Cross-Coupling. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043−3045. 15: (e) Sun, H.; DiMagno, S. G. Room-Temperature Nucleophilic Aromatic Fluorination: Experimental and Theoretical Studies. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720−2725. 16 and **17**: (f) Ruan, J.; Saidi, O.; Iggo, J. A.; Xiao, J. Direct Acylation of Aryl Bromides with Aldehydes by Palladium Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 10510−10511. 18: (g) Yin, H.; Zhao, C.; You, H.; Lin, K.; Gong, H. Mild Ketone Formation via Ni-Catalyzed Reductive Coupling of Unactivated Alkyl Halides with Acid Anhydrides. *Chem. Commun.* **2012**, *48*, 7034−7036. **19**: (h) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. The Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Ynones with Azomethine Ylides. *Org. Lett.* **2011**, *13*, 4680−4683. **20**: (i) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. Rhodium-Catalyzed Allyl Transfer from Homoallyl Alcohols to Aldehydes via Retro-Allylation Followed by Isomerization into Ketones. *Org. Lett.* **2006**, *8*, 2515−2517. **21**: (j) De Houwer, J.; Abbaspour, T.; Kourosch, M.; Bert, U. W. Synthesis of Aryl(di)azinyl Ketones through Copper- and Iron-catalyzed Oxidation of the Methylene Group of Aryl(di)-azinylmethanes. *Angew. Chem., Int. Ed.* **2012**, *51*, 2745−2748. **22**: (k) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. Pd-Catalyzed Copper-Free Carbonylative Sonogashira Reaction of Aryl Iodides with Alkynes for the Synthesis of Alkynyl Ketones and Flavones by Using Water as a Solvent. *J. Org. Chem.* **2005**, *70*, 6097−6100. **23**: (l) Vale, J. R.; Rimpilainen, T.; Sievanen, E.; Rissanen, K.; Afonso, C. A. M.; Candeias, N. R. Pot-Economy Autooxidative Condensation of 2-Aryl-2-lithio-1,3-dithianes. *J. Org. Chem.* **2018**, *83*, 1948−1958. **24:** (m) Prechter, A.; Henrion, G.; Faudot, B.; Pierre; Gagosz, F. Gold-Catalyzed Synthesis of Functionalized Pyridines by Using 2H-Azirines as Synthetic Equivalents of Alkenyl Nitrenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959−4963. **25**: (n) Heller, S. T.; Newton, J. N.; Fu, T.; Sarpong, R. One-pot Unsymmetrical Ketone Synthesis Employing a Pyrrole-Bearing Formal Carbonyl Dication Linchpin Reagent. *Angew. Chem., Int. Ed.* **2015**, *54*, 9839−9843.

https://doi.org/10.1021/acsomega.2c06756
ACS Omega 2022, 7, 48476−48483