Selective α-Methylation of Aryl Ketones Using Quaternary Ammonium Salts as Solid Methylating Agents

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ABSTRACT: We describe the use of phenyl trimethylammonium iodide (PhMe3NI) as an alternative methylating agent for introducing a CH3 group in α-position to a carbonyl group. Compared to conventional methylating agents, quaternary ammonium salts have the advantages of being nonvolatile, noncancerogenic, and easy-to-handle solids. This regioselective method is characterized by ease of operational setup, use of anisole as green solvent, and yields up to 85%.

INTRODUCTION

Incorporating a methyl group into small organic or bioactive molecules can positively affect their physical properties and biological effectiveness.1,2 The latter feature is commonly referred to as the "magic methyl effect".3 This renders the methyl group a prevalent structural motif in small-molecule drugs.4,5 Owing to its considerable impact, a late-stage introduction of a CH3 group has become a particularly promising strategy in drug discovery.6–8 Hence, the development of efficient and new strategies for selective methylation attracts broad interest in medicinal chemistry and basic research, respectively.9–13

Traditionally applied methylating agents often suffer from inconvenient physical properties (e.g., MeBr, b.p. 4 °C, MeI, b.p. 42 °C) or high toxicity (e.g., MeI, Me2SO4). Several organometallic reagents used for methylation (e.g., MeB(OH)2, Me2Sn, Me2Al, MeMgCl, or Me2Zn) are quite challenging to handle, as some are air-sensitive, show low functional group tolerance, or have to be freshly prepared.14,15 These toxicological and safety concerns encouraged us to search for a novel, safe, and easy-to-handle reagent for direct methylation. From previous findings in our group, we established different quaternary ammonium salts as alkylating agents in metal-catalyzed C–H activation reactions.16,17

The predominant role of quaternary ammonium salts in organic reactions is their application as phase transfer catalysts18 and ionic liquids.19 However, their use as alkylating agents in general and methylating agents in particular is quite an unexplored field. There are a few reports on O-methylation of phenolic compounds with tetramethylammonium chloride (Me4NCl, Figure 1, I)20,21 or hydroxide (Me4NOH)22 and phenyl trimethylammonium (PhMe3NCl) chloride.21 N-Methylation via ammonium salts was achieved in azahetero-

Figure 1. Methylation strategies using quaternary ammonium salts.
cycles using tetramethylammonium bromide (Me₄NBr)²³ and more recently in amides, N-heterocycles, alcohols, and thiols using tetramethylammonium fluoride (Me₄NF, Figure 1, II).²⁴ Direct methylation of C(sp²)−H bonds using phenyltrimethylammonium iodide and bromide as methyl source was realized by Uemura et al.²⁵ under NiII-catalysis (Figure 1, III).

With the below-described novel, safe, and metal-free method for α-methylation, we want to set a starting point in the relatively uncharted field of using quaternary ammonium salts as alkylating agents for C(sp³)−H bonds (Figure 1, IV).

## RESULTS AND DISCUSSION

We started by investigating the methylation of benzyl 4-fluorophenyl ketone 1a since quantification in all optimization steps can be accomplished via ¹⁹F NMR using trifluoro toluene as internal standard without preceding workup or solvent removal. Initially, Me₂NBr was used as the methyliating agent and KOH as the base in toluene at 130 °C. Here, we observed the methyl enol ether 2a and the α-methylated product 3a forming in a 1.2:1 ratio (Table 1, Entry 1). In a next step, it was investigated whether switching the solvent could shift the product distribution toward the desired product 3a. Since the process should be as benign as possible, we aimed to find a suitable green solvent in combination with an inexpensive base. 2-Methyl-THF, anisole,²⁶ and cyclopentylmethylether²⁷ are considered green solvents and were tested (among others; see the SI for full list) in this transformation. Anisole (entry 3) showed the highest overall conversion and additionally slightly favored the desired product 3a (entry 3, 1:1.08 ratio of 2a and 3a). 2-Methyl-THF and cyclopentylmethylether gave lower conversion and additionally favored the undesired product 2a (entries 2 and 4). Other benign solvents proved to be inefficient (see complete solvent screening list in the SI). We further investigated the influence and efficiency of different bases. Hydroxy bases gave the best yields, with the initially used KOH surpassing NaOH. KO'Bu and Cs₂CO₃ showed significantly lower conversion. The other bases tested turned out to be inefficient (see the SI for details).

Before continuing with optimization of the methylaing reagent, it was tested whether the O- and the α-methylated products 2a and 3a are formed independently or whether 2a might be the actual methylaing agent. The kinetic profile showed that both the O- and the α-methylated product are formed simultaneously under the given reaction conditions within 30 minutes, and no shift in product ratio could be observed at prolonged reaction times (see Figure 2).

Figure 2. Reaction time screening; conditions: Me₄NBr (1.5 equiv), KOH (2 equiv), anisole (0.2 M), 130 °C.

And finally, a 1:1 mixture of 1a and 2a was subjected to the reaction conditions in the absence of Me₂NBr without any formation of 3a. This excludes that the two products are interconvertible under the applied conditions and are indeed formed independently (cf. Table 2).

| entry | solvent | ammonium salt | 1a | 2a | 3a |
|-------|---------|---------------|----|----|----|
| 1     | toluene | Me₂NBr        | 0  | 41 | 34 |
| 2     | MeTHF  | Me₂NBr        | 25 | 14 | 11 |
| 3     | anisole| Me₂NBr        | 0  | 40 | 43 |
| 4     | CPME   | Me₂NBr        | 4  | 36 | 24 |
| 5     | anisole| Me₂NCl        | 0  | 43 | 42 |
| 6     | anisole| Me₂NI         | 30 | 23 | 29 |
| 7     | anisole| Me₂NOAc       | 0  | 49 | 9  |
| 8     | anisole| PhMe₂NCl      | 0  | 47 | 48 |
| 9     | anisole| PhMe₂NBr      | 0  | 38 | 50 |
| 10    | anisole| PhMe₂NI       | 0  | 18 | 78 |
| 11    | anisole| Bu₂Me₂NCl     | 6  | 25*| 39 |
| 12    | anisole| Bu₂Me₂NBr     | 0  | 47 | 25 |
| 13    | anisole| PhMe₂NBr      | 0  | 47 | 25 |

α-methylation.
Next, we screened for different ammonium salts as methyl sources. We found that \(\text{Me}_4\text{NCl} \) and \(\text{Me}_4\text{NBr} \) gave equal yields and product ratios, whereas \(\text{Me}_3\text{NI} \) gave incomplete conversion (entries 5 and 6). Tetramethylammonium acetate favored the \(\text{O}-\text{methyl} \) enol ether (entry 7). When using ammonium salts with different substituents on the quaternary nitrogen, we observed additional \(\text{O}-\text{butylation} \) (13%) with \(\text{Bu}_3\text{MeNCl} \) (entry 11) and mainly \(\alpha\)-benzylolation (64%) with \(\text{BnMe}_3\text{NCl} \) (entry 12). When using \((\text{C}_{16}\text{H}_{33})\text{Me}_3\text{NBr} \) as an alkylating agent, only 2a and 3a were formed, but no hexadecylated compound of any kind (entry 13). The naturally occurring ammonium salt betaine was practically ineffective (entry 14). Gratifyingly, we identified phenyl trimethylammonium salts giving significantly higher overall yields. Going from the chloride and bromide to the iodide salt, we observed a shift towards the desired \(\alpha\)-methylated product 3a (entries 8–10). Compared with tetramethylammonium salts, a phenyl substituent on the ammonium most probably withdraws electron density from the adjacent methyl substituents, which then, in turn, are more prone to react with the "soft" \(\alpha\)-carbon of the enolate rather than being attacked by the carbonyl oxygen. Finally, we found the optimal reaction conditions being PhMe_3NI (1.5 equiv) and KOH (2 equiv) in anisole (0.2 M) at 130 °C, 1h.

| entry | \(\text{Me}_4\text{NBr} \) (2 equiv) | yield (%) |
|-------|-----------------------------------|----------|
| 1     | 0.093                             | 42       |
| 2     | 0.047                             | 73       |
| 3     | 0.088                             | 86       |
| 4*    |                                  | 44       |
*The reaction was performed in the absence of the methylating agent \((\text{Me}_4\text{NBr})\). bYield was determined by \(^{19}\text{F NMR} \) using trifluoro toluene as internal standard.

With the optimized reaction conditions in hand, we performed \(\alpha\)-methylolation reactions on various substrates to demonstrate the scope of this direct transformation (Scheme 1). In this reaction \(\text{N,N-Dimethylalanine} \) is formed stoichiometrically from the methylating agent PhMe_3NI. This byproduct, however, can be easily quenched \textit{in situ} and fully separated from the desired product in form of its water-soluble HCl salt by a mild acidic workup procedure. The desired methylated compounds were obtained in isolated yields up to 85%. Interestingly, the formation of any \(\alpha\)-\(\alpha\)-dimethylated products was never observed. We performed the methylation of benzyl 4-fluorophenyl ketone 1a on a 1.4 mmol scale to prove the scalability of this method. The desired product 3a was isolated in a yield of 85%. Significantly lower yields were observed for the sterically more hindered substrate 1-(pentamethylphenyl)-2-phenylethanone (product 3d). Substrates that are less susceptible to enolization, \textit{e.g.}, 4-phenylcyclohexanone 3t, also resulted in diminished yields, and mainly starting material was recovered. A variety of functional groups, including halides (products 3a, 3e, 3f, and 3q), CF_3 (product 3i), ether (products 3g & 3h, 3m−3p), and

| entry | substrate | yield (%) |
|-------|-----------|----------|
| 1a    | 2a        | 42       |
| 2a    | 3a        | 9        |
| 3a    |           | 44       |
Phenyl groups (product 3r) were well tolerated in different positions of the aryl ring. Substrates bearing even more reactive functional groups on the aryl ring, e.g., ester moieties, can also be methylated in moderate yields (product 3v and 3w). As assumed, when 1-(4-hydroxyphenyl)-2-phenylethanone was subjected to the respective conditions, methylation initially occurred at the phenolic oxygen, and subsequently at the α-position of the carbonyl (product 3x and 3p). Our method, however, is not only limited to bisaromatic compounds but can also be applied for monoaromatic substrates. 4-Methyl-1-phenyl-2-pentanone was methylated regioselectively at the benzylic position giving product 3u in 77% yield. Aliphatic ketones without any benzylic α-carbons, e.g., 8-pentadecanone, formed only the aldol product and hence are not mentioned in this paper. As a proof of concept, we performed late-stage methylation of the biologically active compound fenbufen. Herein, the carboxylic acid moiety is preferentially methylated (product 3y). Upon addition of fresh reagent after prolonged reaction times, however, the fenbufen methyl ester could be further methylated at the α-position (product 3z; see the SI for details).

Finally, we wanted to briefly outline the applicability of this new protocol for introducing larger substituents than methyl. Selective α-ethylation can be accomplished accordingly, using phenyltriethylammonium iodide (PhEt₃NI) as the alkyl source. Benzyl 4-fluorophenyl ketone 1a was successfully ethylated at the α-position in 78% yield using PhEt₃NI (product 4a). Substrates containing electron-donating substituents on the aryl ring (product 4b), as well as monoaromatic compounds (product 4c) can also be ethylated in yields of 68 and 57%, respectively.
respectively. Benzylation is of interest since the phenyl benzyl ketone motif can be found in several drugs or promising drug candidates, as, for example, desoxybenzoyl derivatives or ring-truncated deguelin analogues. SAR studies identified the latter as promising candidates for HIF-1α inhibitors. One of those analogues, SH-1242, further inhibits Hsp90 activity and shows potent anticaner efficacy. We could demonstrate the applicability of this method for benzylation of selected substrates using BnMe3NCl as a benzylation agent. Products 5a–5c were obtained in high yields of 84, 89, and 78%, respectively. Since methylating agents, however, are by far more hazardous than traditionally applied ethylating and benzylation reagents, we did not further investigate the latter strategies.

## Conclusions

In conclusion, we described the use of quaternary ammonium salts as alternative alkylating and benzylation agents. Phenyl trimethylammonium iodide and related salts were successfully established as selective, highly efficient, safe, and easy-to-handle methylating reagents for direct C(sp²)–C(sp³) bond formation.

## Experimental Section

**General.** All chemicals were purchased from commercial suppliers and, unless noted otherwise, used without further purification. NaOBU(2.6 mmol, 1.3 equiv), Pd2(dba)3 (5 mol %), and DPE-Phos (10 mol %), THF (2 mL, 1 M) was added, and the dark brownish-green mixture was stirred for 5 min at ambient temperatures. The aryl bromide (2 mmol, 1 equiv) was added via Eppendorf pipette, followed by rapid addition of the acetonaphene (2.4 mmol, 1.2 equiv) in one portion as solid or via Eppendorf pipette if liquid. Immediate solid formation could be observed. The vial was closed with a Wheaton screw cap and transferred out of the glovebox.

**General Procedure B for Precursor Synthesis.** In the glovebox, a flame-dried 8 mL glass vial equipped with a magnetic stirring bar was charged with NaOBU (2.6 mmol, 1.3 equiv), Pd2(dba)3 (5 mol %), and DPE-Phos (10 mol %), THF (2 mL, 1 M) was added, and the dark brownish-green mixture was stirred for 5 min at ambient temperatures. The aryl bromide (2 mmol, 1 equiv) was added via Eppendorf pipette, followed by rapid addition of the acetonaphene (2.4 mmol, 1.2 equiv) in one portion as solid or via Eppendorf pipette if liquid. Immediate solid formation could be observed. The vial was closed with a Wheaton screw cap and transferred out of the glovebox.

The mixture was heated to 70 °C in a metallic reaction block and stirred for 2–18 h at respective temperatures. After complete consumption of the starting material (GC-MS monitoring), water (10 mL) was added and the mixture was extracted three times with diethyl ether (30 mL each). The combined organic phases were washed once with sat. NaHCO3 solution and then with brine, dried over anhydrous Na2SO4, filtered, and concentrated. The crude product was purified via gradient flash column chromatography on silica gel using a mixture of light petroleum (LP) and EtOAc.

**1-(3,4-Dimethoxyphenyl)-2-phenylethanone 37 (1g).** Prepared following the general procedure B from 3,4-dimethoxacetophenone and bromobenzene heated for 2 h. The crude product was purified via flash column chromatography (50 g silica, LP:EtOAc 100:1) to yield 443 mg (86%) of the title compound as a yellow oil. **19F NMR (400 MHz, CDCl3): δ = −196.3, 135.3, 149.1, 135.1, 129.7, 129.3, 128.6, 128.5, 123.5, 110.7, 105.0, 55.9, 45.2.**

**Optimization Screening.** The optimization of reaction conditions was conducted following the general procedure A (see the SI for details). Yields were determined by 19F NMR using trifluoro toluene as internal standard.

### 1-Fluoro-4-(1-methoxy-2-phenylethenylene)benzene 66 (2a). An 8 mL glass vial equipped with a magnetic stirring bar was charged with benzyl 4-fluorophenyl ketone (1) (100 mg, 0.467 mmol, 1 equiv), MeNBr (119 mg, 770 mmol, 1.65 equiv), and KOH (79 mg, 1.4 mmol, 3 equiv). The vial was sealed with a septum screw cap. Using a cannula, the vial was evacuated and backfilled with argon three times. The toluene (2 mL, 0.23 M) was added via a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block. After 18 h at respective temperatures, the reaction was cooled to room temperature and solids were centrifuged off. The supernatant solution was transferred to a round-bottom flask, and the solid residue was washed three times with small amounts DCM. The combined organic phases were concentrated. The crude oil was further purified via hand column chromatography (5 g silica LP:Et_N 100:1) to yield 46 mg (43%) of the title compound as white crystals. **1H NMR (400 MHz, CDCl3): δ = 7.74−7.67 (m, 2H), 7.60−7.50 (m, 2H), 7.37−7.25 (m, 2H), 7.19 (m, 1H), 7.16−7.03 (m, 2H), 6.06 (s, 1H), 3.63 (s, 3H).** **13C{1H} NMR (101 MHz, CDCl3): δ = 163.0 (d, J = 247.9 Hz), 155.4, 135.9, 132.6 (d, J = 3.3 Hz), 128.7, 128.6, 128.5 (d, J = 8.1 Hz), 126.8, 115.6 (d, J = 21.7 Hz), 112.8 (d, J = 1.4 Hz), 58.0.** **19F NMR (376 MHz, CDCl3): δ = −113.2 HRMS (ESI): m/z [M + H]^+ calc for C13H12FO: 229.1023; found: 229.1000.**

**Figure 1.** Flash column chromatography on silica gel using a mixture of light petroleum (LP) and EtOAc.

**1-(3-Methoxyphenyl)-2-phenylethanone 38 (1I).** Prepared following the general procedure B from 3-(trimethoxymethyl)phenylacetophenone and bromobenzene heated for 3 h. The crude product was purified via flash column chromatography (50 g silica, LP:EtOAc 100:1) to yield 525 mg (78%) of the title compound as white crystals. **1H NMR (400 MHz, CDCl3): δ = 7.58 (d, J = 2.1 Hz, 1H), 7.39−7.22 (m, 5H), 6.89 (d, J = 8.4 Hz, 1H), 4.26 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H).** **13C{1H} NMR (100 MHz, CDCl3): δ = 196.3, 153.3, 149.1, 135.1, 129.7, 129.3, 128.6, 128.5, 123.5, 110.7, 110.0, 55.9, 45.2.**

**1-(3-Methoxyphenyl)-2-phenylethanone 39 (1H).** Prepared following the general procedure B from 3-trifluromethyloxyacetophenone and bromobenzene heated for 4 h. The crude product was purified via flash column chromatography (90 g silica, LP, and EtOAc 0–15%) to yield 391 mg (74%) of the title compound as an orange oil. **1H NMR (400 MHz, CDCl3): δ = 8.26 (tt, J = 1.8, 0.8 Hz, 1H), 8.16 (dt, J = 7.3, 1.1 Hz, 1H), 7.81−7.70 (m, 1H), 7.56 (tt, J = 7.9, 0.8 Hz, 1H), 7.38−7.29 (m, 2H), 7.29−7.18 (m, 3H), 4.29 (s, 2H).** **13C{1H} NMR (100 MHz, CDCl3): δ = 196.3, 137.1, 133.9, 131.9 (d, J = 1.4 Hz), 131.2 (q, J = 34.0 Hz), 129.6 (q, J = 3.6 Hz), 129.5...
Methyl 4-(2-Oxo-2-phenylethyl)benzoate (1v). Prepared following the general procedure B from acetoephonone methyl 4-isobutylbenzene heated for 4 h. The crude product was purified via flash column chromatography (90 g silica, LP, and EtOAc 0–20%) to yield 285 mg (37%) of the title compound as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.04 – 7.98$ (m, 4H), 7.62 – 7.54 (m, 1H), 7.51 – 7.44 (m, 2H), 7.37 – 7.32 (m, 2H), 4.35 (s, 2H), 3.90 (s, 3H). $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta = 196.9, 167.0, 139.9, 136.5, 133.5, 130.0, 129.7, 129.0, 128.8, 128.6, 77.4, 52.2, 45.5.

Ethyl 4-(2-Phenyl-2-propenyl)benzoate (1w). Prepared following the general procedure B from acetoephonone ethyl 4-isobutylbenzene heated for 4 h. The crude product was purified via flash column chromatography (90 g silica, LP), and EtOAc 0–20% to yield 360 mg (45%) of the title compound as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.04 – 7.97$ (m, 4H), 7.62 – 7.53 (m, 1H), 7.51 – 7.42 (m, 2H), 7.37 – 7.31 (m, 2H), 4.41 – 4.31 (m, 4H), 1.38 (t, $J = 7.1$ Hz, 3H). $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta = 196.9, 166.5, 139.8, 136.5, 133.0, 129.6, 128.8, 128.6, 61.0, 45.5, 14.4.

General Procedure C for Methylation, Ethylation, and Benzylations Reactions. An 8 mL glass vial equipped with a magnetic stirring bar was charged with the respective diaryl ethanoate (100 mg, 1 equiv), the ammonium salt (1.1 for BnMe$_3$NCl or 2 equiv for PhMe$_3$NI and PhEt$_3$NI), and KOH (2 equiv). The vial was sealed with a septum screw cap, the vial was evacuated and backfilled with argon three times. Anisole (2 mL, 0.2 M) was added via a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 2–4 h. After complete consumption of the starting material (TLC analysis), the reaction was cooled to room temperature. HCl (2 N, 2 mL) was added, and the mixture was extracted three times with EtOAc (5 mL each). The combined organic phases were washed twice with 2 N HCl (1 mL each) and once with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. For benzylation reactions, the mixture was not subjected to aqueous workup but filtered over a short plug of silica, washed with EtOAc, and concentrated. The obtained crude product was purified via hand column with an unmodified silica.

1-(4-Fluorophenyl)-2-phenyl-1-propanone (3a). Prepared following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified via column chromatography (8 g silica LP/EtOAc 50:1, 45:1, 40:1) to yield 83 mg (78%) of the title compound. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.49$ (d, $J = 1.7$ Hz, 1H), 7.39 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.03 (s, 2H), 4.21 (s, 2H). $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta = 195.8, 151.9, 148.3, 134.9, 131.5, 129.4, 128.7, 128.6, 134.1, 112.4, 54.5.

2-(3-Methoxyphenyl)-1-phenylethanol (10o). Prepared following the general procedure B from acetophenone and 4-bromoanisole heated for 18 h. The crude product was purified via flash column chromatography (90 g silica, LP, and EtOAc 0–40%) to yield 257 mg (59%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.06 – 7.97$ (m, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.25 (t, $J = 7.8$ Hz, 1H), 6.91 – 6.77 (m, 3H), 4.26 (s, 2H), 3.79 (s, 3H). $^{13}$C{H} NMR (101 MHz, CDCl$_3$): $\delta = 197.5, 159.8, 136.6, 136.1, 133.2, 129.7, 128.7, 121.9, 115.2, 112.4, 55.2, 45.6.

2-(4-Fluorophenyl)-1-phenylethanol (1aq). Prepared following the general procedure B from acetophenone and 1-bromo-4-fluorobenzene heated for 18 h. The crude product was purified via flash column chromatography (90 g silica, LP, and EtOAc 0–40%) to yield 255 mg (60%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.12 – 8.04$ (m, 2H), 7.70 – 7.64 (m, 2H), 7.64 – 7.59 (m, 2H), 7.50 – 7.43 (m, 2H), 7.43 – 7.22 (m, 4H), 4.31 (s, 2H). $^{13}$C{H} NMR (100 MHz, CDCl$_3$): $\delta = 197.2, 145.8, 139.8, 135.3, 134.7, 129.5, 129.3, 129.0, 128.7, 128.3, 127.3, 127.3, 126.9, 45.6.
1,2-Diphenyl-1-propanone 45 (3b). Prepared following the general procedure C from commercially available starting material with a reaction time of 3 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1, 40:1) to yield 73 mg (68%) of the title compound as a colorless oil. 1H NMR (400 MHz, CDCl3): δ = 8.01–7.93 (m, 2H), 7.53–7.43 (m, 1H), 7.43–7.34 (m, 2H), 7.30 (d, J = 4.3 Hz, 4H), 7.21 (dd, J = 8.8, 4.3, 3.9 Hz, 1H), 4.70 (q, J = 6.9 Hz, 1H), 1.55 (d, J = 6.9 Hz, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ = 200.4, 141.6, 136.6, 132.9, 129.1, 128.9, 128.6, 127.9, 127.0, 48.0, 19.6. 2-(4-Methylphenyl)-1-phenyl-1-propanone 45 (3c). Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1) to yield 76 mg (74%) of the title compound as a yellowish oil. 1H NMR (400 MHz, CDCl3): δ = 8.01–7.94 (m, 2H), 7.52–7.43 (m, 1H), 7.43–7.34 (m, 2H), 7.23–7.16 (m, 2H), 7.15–7.08 (m, 2H), 4.67 (q, J = 6.8 Hz, 1H), 2.30 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ = 200.5, 138.6, 136.6, 132.8, 129.8, 128.9, 128.6, 127.7, 46.7, 21.1, 19.6. HRMS (ESI): m/z [M + H]+ calcd for C15H14BrO: 289.0218; found: 289.0218. Preparing the general procedure C from compound 1i with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1) to yield 76 mg (74%) of the title compound as a yellowish oil. 1H NMR (400 MHz, CDCl3): δ = 7.93–7.85 (m, 2H), 7.35–7.25 (m, 2H), 7.18–7.12 (m, 2H), 4.69 (q, J = 6.9 Hz, 1H), 2.48 (d, J = 7.2 Hz, 2H), 1.85 (d, J = 13.4 Hz, 1H), 1.54 (d, J = 6.9 Hz, 3H), 0.88 (dd, J = 6.6, 0.6 Hz, 6H). 13C{1H} NMR (101 MHz, CDCl3): δ = 200.0, 147.3, 141.7, 134.3, 129.3, 128.9, 128.7, 126.8, 47.7, 45.4, 30.1, 22.4, 22.3, 19.6. HRMS (ESI): m/z [M + H]+ calcd for C24H28BrO2: 579.1099; found: 579.1102. 1-(4-Methylphenyl)-2-phenyl-1-propanone 45 (3d). Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1) to yield 87 mg (85%) of the title compound. 1H NMR (400 MHz, CDCl3): δ = 7.92–7.84 (m, 2H), 7.38–7.16 (m, 7H), 4.62 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ = 199.1, 141.3, 139.3, 134.9, 130.3, 129.3, 128.9, 127.8, 127.2, 48.2, 19.5. HRMS (ESI): m/z [M + H]+ calcd for C15H14BrO: 289.0218; found: 289.0218. Preparing the general procedure C from compound 1g with a reaction time of 3 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1) to yield 75 mg (74%) of the title compound. 1H NMR (400 MHz, CDCl3): δ = 7.84–7.76 (m, 2H), 7.56–7.46 (m, 3H), 7.36–7.25 (m, 3H), 7.25–7.16 (m, 4H). 13C{1H} NMR (101 MHz, CDCl3): δ = 199.1, 141.3, 135.2, 131.9, 130.4, 129.2, 128.0, 127.8, 127.2, 48.2, 19.5. HRMS (ESI): m/z [M + H]+ calcd for C14H13BrO: 267.1739; found: 267.1739. 1-(3,4-Dimethoxyphenyl)-2-phenyl-1-propanone 46 (3g). Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 50:1, 40:1, 10:1) to yield 72 mg (68%) of the title compound. Rf = 0.54 (LP/EtOAc 2:1). 1H NMR (400 MHz, CDCl3): δ = 7.59 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 4.4 Hz, 4H), 7.19 (dd, J = 8.6, 4.9, 3.9 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 4.65 (q, J = 6.9 Hz, 1H), 3.88 (d, J = 4.1 Hz, 2H), 1.52 (d, J = 6.8 Hz, 3H). 13C{1H} NMR (101 MHz, CDCl3): δ = 199.0, 153.1, 149.0, 142.2, 129.7, 129.1, 127.7, 126.9, 123.5, 111.1, 110.0, 56.1, 56.0, 47.6, 19.7. HRMS (ESI): m/z [M + H]+ calcd for C19H18O2: 271.1329; found: 271.1329. 1-(3-Methoxyphenyl)-2-phenyl-1-propanone 47 (3h). Prepared following the general procedure C from compound 1h with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, LP/EtOAc 70:1) to yield 88 mg (83%) with a reaction time of 2 h.
(101 MHz, CDCl₃): δ = 198.5, 151.6, 148.2, 141.9, 131.4, 129.1, 127.8, 127.0, 125.1, 108.7, 107.9, 101.9, 47.8, 19.7. HRMS (ESI): m/z [M + H]⁺ calcd for C₂₃H₂₂O₂: 283.1329; found: 283.1328

2-(3-Methoxyphenyl)-1-phenyl-1-propanone⁵⁵ (3t). Prepared following the general procedure C from commercially available starting material with a reaction time of 18 h. The crude product was purified via column chromatography (8 g silica, L/P/EtOAc 80:1-10:1) to yield 18 mg (17%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.33–7.32 (m, 2H), 7.32–7.14 (m, 3H), 3.10 (t, J = 12.4, 3.5 Hz, 1H), 2.64–2.53 (m, 1H), 2.53–2.42 (m, 2H), 2.26–2.14 (m, 2H), 1.98–1.81 (m, 1H), 1.69–1.57 (m, 1H), 1.03 (d, J = 6.5 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ = 161.4, 145.3, 135.5, 132.9, 132.8, 128.7, 127.3, 127.2, 127.0, 48.0, 19.6. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₂H₁₀O: 173.0678; found: 173.0680.

Ethyl 4-(1-Methyl-2-oxo-2-phenylethyl)benzoate⁵⁶ (3w). Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified via flash column chromatography (15 g silica, L/P/EtOAc 20:1, 1:1) to yield 15 mg (9%) of the title compound as a BOIL oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.36–7.27 (m, 2H), 7.29–7.19 (m, 1H), 7.21–7.16 (m, 2H), 3.71 (q, J = 7.0 Hz, 1H), 2.30–2.15 (m, 2H), 2.09 (dp, J = 13.4, 6.6 Hz, 1H), 1.38 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ = 150.5, 146.9, 144.8, 133.8, 133.0, 132.8, 129.3, 128.7, 126.8, 113.8, 55.5, 47.6, 19.7. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₄H₁₂O₂: 229.0972; found: 229.0974.

Methyl 3-(4-Phenylcyclohexanone⁵⁷ (3y). Prepared following the general procedure C with the deviation of using only 1 equiv of PhMe₃NI, from commercially available starting material with a reaction time of 2 h. The crude product was purified via flash column chromatography (15 g silica, L/P/EtOAc 70:1–50:1) to yield 68 mg (64%) of the title compound as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.61–7.55 (m, 4H), 7.48–7.42 (m, 2H), 7.37–7.31 (m, 2H), 1.57 (d, J = 6.9 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ = 199.5, 145.0, 137.2, 135.6, 131.0, 129.7, 128.7, 126.8, 113.8, 55.5, 47.6, 19.7. HRMS (ESI): m/z [M + H]⁺ calcd for C₁₄H₂₁O: 229.0936; found: 229.0937.

1-(1,1’-Biphenyl-4-yl)-2-phenyl-1-propanone⁵⁸ (3z). Prepared following the general procedure C from commercially available starting material with a reaction time of 2 h. The crude product was purified via column chromatography (8 g silica, L/P/EtOAc 80:1) to yield 82 mg (77%) of the title compound as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.71–7.63 (m, 9H), 7.44–7.36 (m, 9H), 4.26 (s, J = 6.8 Hz, 2H), 4.23 (s, J = 6.8 Hz, 2H), 4.03 (s, 3H), 3.87 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H), 1.22 (m, 4H), 0.85 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃): δ = 146.3, 132.8, 131.0, 129.3, 128.7, 126.8, 113.8, 55.5, 47.6, 19.7. HRMS (ESI): m/z [M + H]⁺ calcd for C₂₂H₂₁O: 309.1512; found: 309.1509.
0.2 M) was added via a syringe. Evacuation and backfilling with argon were repeated three times under vigorous stirring that no boiling delay occurred. Subsequently, the septum screw cap was exchanged for a closed Wheaton cap, and the vial was sealed tightly. The resulting inhomogeneous mixture was heated to 130 °C in a metallic heating block for 3 h. The reaction mixture was cooled to room temperature, and additional PhMe3NI (2 equiv) and KOH (2 equiv) were added. Subsequently, the reaction was heated up to 130 °C and stirred for 4 days (with further addition of 2 equiv PhMe3NI and 2 equiv KOH after 48 h). The reaction was cooled to room temperature. HCl (2 N, 2 mL) were added, and the mixture was extracted three times with EtOAc (20 mL each). The combined organic phases were washed twice with 2 N HCl (3 mL each) and once with brine, dried over anhydrous Na2SO4, and concentrated. The obtained crude product was purified via column chromatography (15 g silica, LP/EtOAc 30:1) to yield 121 mg (89%) of the title compound. 

1H NMR (400 MHz, CDCl3): δ = 7.99–7.89 (m, 2H), 7.32–7.13 (m, 8H), 7.13–7.06 (m, 2H), 7.05–6.96 (m, 2H), 4.78 (t, J = 7.2 Hz, 1H), 3.58 (dd, J = 13.7, 7.5 Hz, 1H), 3.08 (dd, J = 13.7, 7.0 Hz, 1H).

13C{1H} NMR (100 MHz, CDCl3): δ = 197.7, 165.6 (d, J = 254.9 Hz), 139.7, 139.0, 133.2 (d, J = 3.0 Hz), 131.4, 131.3, 129.2, 129.1, 128.3 (d, J = 4.6 Hz), 127.3, 126.3, 115.6 (d, J = 21.9 Hz), 56.0, 40.2.

HRMS (ESI): m/z [M + H]+ calced for C14H21O: 205.1587; found: 205.1593.

1,2-Bis-[4-(methylthio)-phenyl]-2-phenyl-1-butane56 (4b). Prepared following the general procedure C, except for the use of PhMe3NI (2 equiv) instead of PhMe3NI, from commercially available starting material with a reaction time of 2 h. The crude product was purified via column chromatography (15 g silica, LP/EtOAc 100:1–100:3) to yield 115 mg (78%) of the title compound as white crystals.

1H NMR (400 MHz, CDCl3): δ = 7.47–7.29 (m, 7H), 7.29–7.23 (m, 7H), 7.22–7.16 (m, 3H), 4.07–3.98 (m, 1H), 3.56 (dd, J = 13.7, 7.9, 1.6 Hz, 1H), 3.03 (dd, J = 13.7, 6.8, 1.4 Hz, 1H), 2.29 (dt, J = 6.3, 1.3 Hz, 2H), 2.25–2.09 (m, 0.89) (dd, J = 6.6, 1.2 Hz, 3H), 0.79 (dd, J = 6.5, 1.2 Hz, 3H).

13C{1H} NMR (100 MHz, CDCl3): δ = 209.3, 139.9, 138.5, 129.1, 128.9, 128.5, 128.0, 127.3, 127.1, 126.1, 61.3, 51.4, 38.7, 24.2, 22.6, 22.1. HRMS (ESI): m/z [M + H]+ calced for C14H21O2: 243.1180; found: 243.1186.

1,2-Bis-4-methylthio-phenyl-1-butane56 (4b). Prepared following the general procedure C, except for the use of PhEt3NI (2 equiv) instead of PhMe3NI, from commercially available starting material with a reaction time of 2 h.

1H NMR (400 MHz, CDCl3): δ = 7.99–7.89 (m, 2H), 7.32–7.13 (m, 8H), 7.13–7.06 (m, 2H), 7.05–6.96 (m, 2H), 4.78 (t, J = 7.2 Hz, 1H), 3.58 (dd, J = 13.7, 7.5 Hz, 1H), 3.08 (dd, J = 13.7, 7.0 Hz, 1H).

13C{1H} NMR (100 MHz, CDCl3): δ = 197.7, 165.6 (d, J = 254.9 Hz), 139.7, 139.0, 133.2 (d, J = 3.0 Hz), 131.4, 131.3, 129.2, 129.1, 128.3 (d, J = 4.6 Hz), 127.3, 126.3, 115.6 (d, J = 21.9 Hz), 56.0, 40.2.

HRMS (ESI): m/z [M + H]+ calced for C14H21O: 205.1587; found: 205.1593.

1,2-Bis-[4-methylthio]-2,3-diphenyl-propan-1-one50 (5b). Prepared following the general procedure C, except for the use of PhMe3NI (1.1 equiv) instead of PhMe3NI, from commercially available starting material with a reaction time of 2 h.

1H NMR (400 MHz, CDCl3): δ = 7.96–7.87 (m, 2H), 7.24–7.11 (m, 5H), 7.11–7.04 (m, 2H), 6.87–6.75 (m, 4H), 4.72 (t, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.53 (dd, J = 13.7, 7.3 Hz, 1H), 3.04 (dd, J = 13.7, 7.2 Hz, 1H).

13C{1H} NMR (100 MHz, CDCl3): δ = 198.0, 163.3, 158.6, 140.1, 131.6, 131.0, 129.8, 129.3, 129.2, 128.2, 128.1, 114.3, 113.7, 55.5, 55.2, 54.7, 40.2. HRMS (ESI): m/z [M + H]+ calced for C14H21O2: 247.1642; found: 247.1650.
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