



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

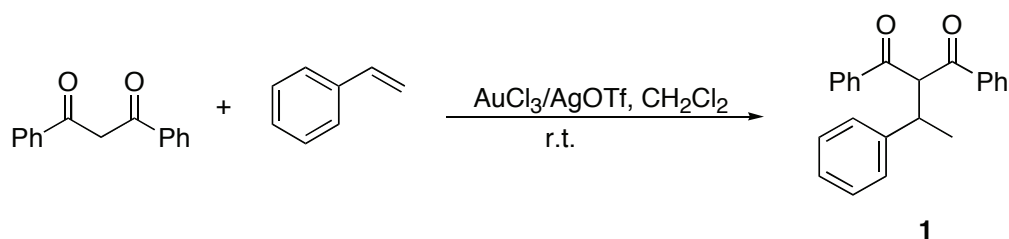
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

HIGHLY EFFICIENT ADDITION OF ACTIVATED METHYLENE COMPOUNDS TO ALKENES CATALYZED BY GOLD AND SILVER



Submitted by Chao-Jun Li¹ and Xiaoquan Yao.

Checked by Brian P. Jones and John A. Ragan.

1. Procedure

1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione. An oven-dried, 300-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber septum, a stopcock and a Teflon-coated magnetic stir bar is cooled to room temperature under a flow of nitrogen. While temporarily removing the septum, the flask is charged with gold(III) chloride (AuCl₃) (0.303 g, 1 mmol, 5 mol% Au) and silver trifluoromethanesulfonate (AgOTf) (0.77 g, 3 mmol, 15 mol%) (Note 1) under N₂. Dichloromethane (150 mL) (Note 2) is added, and the catalyst mixture is stirred at room temperature for 1.5–2 h, resulting in a brown suspension (Note 3). Dibenzoylmethane (4.48 g, 20 mmol) (Note 4) is added to the reaction flask over 2 min while temporarily removing the septum and the color of the reaction mixture turns green. Styrene (3.45 mL, 30 mmol) (Notes 5, 6) is diluted to 25 mL with CH₂Cl₂ and added dropwise to the reaction mixture by syringe pump through the septum over 6–7 h at room temperature (Note 7). The mixture is then stirred for another 30 min (Note 8). A deep-green solution is obtained (Note 9). The solution is filtered through approximately 40 mL of silica gel in a 60-mL glass Büchner filter funnel to remove the catalyst (Note 10). The silica gel is washed with ether (6 x 50 mL), and the filtrate is concentrated by rotary evaporation at room temperature. The residue, a clear, orange-brown oil, is then purified by flash column chromatography (Note 11) to provide the crude product as a pale yellow solid (6.44 g, 98 %) (Note 12). Further purification is achieved by recrystallization. The crude product is dissolved in 30 mL of hot EtOAc, and diluted with 90 mL of hexanes to the point of cloudiness. The mixture

is allowed to cool slowly to room temperature overnight, and the resulting solids are collected by filtration, rinsing with 10 mL of hexanes. The solids are air-dried, then placed in a vacuum oven for 4 h to provide analytically pure product as a white solid (4.16 g, 12.7 mmol, 63%) (Notes 13, 14).

2. Notes

1. Gold(III) chloride (99.99%+) and silver trifluoromethanesulfonate (99%+) were purchased from the Aldrich Chemical Company and used as received.

2. Dichloromethane was purchased from J. T. Baker (HPLC grade) and used as received. The submitters distilled their dichloromethane from CaH_2 .

3. Silver trifluoromethanesulfonate was stirred with gold chloride in dichloromethane, which results in a brown (in some cases orange) precipitate (the clear solution was almost colorless). The clear solution had no catalytic activity.

4. Dibenzoylmethane (98%) was purchased from the Aldrich Chemical Company and used as received.

5. Styrene (99%, inhibited with 10–15 ppm 4-*tert*-butylcatechol) was purchased from the Aldrich Chemical Company and used as received.

6. The main side reaction was the dimerization of styrene, resulting in the formation of 1,3-diphenyl-but-1-ene as the by-product. In order to increase the yield of the major product, excess styrene had to be used. When enlarging the scale of the reaction, the dimerization of styrene became more serious. Therefore, in this case, 1.5 to 2 equiv. of styrene was required.

7. A competition exists between the addition of dibenzoylmethane to styrene and the dimerization of styrene, therefore introduction of styrene in one portion or too quickly resulted in a decreased yield.

8. The submitters stirred the reaction for an additional 4 h. The checkers found that a post-addition stir time ranging from 30 min to 16 h had no impact on product yield or quality.

9. The product was detected by TLC (hexanes/EtOAc = 10/1). R_f (dimer of styrene): 0.91; R_f (diketone): 0.49; R_f (product): 0.29.

10. Length: 3.5 cm diameter \times 4 cm. If the catalyst was not removed before evaporation, the product tended to decompose to the diketone and the dimer of styrene. In a control experiment, when the catalyst was not

removed before evaporation (bath temperature of the rotary evaporator: 50 °C), a lower yield was obtained (4.14 g, 63% yield before recrystallization).

11. The oil was diluted with 50 mL of CH₂Cl₂, and 13 g of SiO₂ (Baker, 40 μm, flash chromatography grade) was added. The resulting slurry was concentrated on the rotary evaporator to a tan powder, which was charged to the top of a column prepared from flash silica gel slurried in 2% EtOAc-hexanes (column dimensions 3.5 cm diameter x 18 cm height). Elution with 2% EtOAc-hexanes (1.5 L, removed unreacted dibenzoylmethane) followed by 10% EtOAc-hexanes (6 L) afforded the product in fractions 19-74 (75 mL fractions were collected). The product-containing fractions were combined and concentrated to provide the crude product.

12. The product at this stage was probably suitable for most subsequent applications (ca. 90% purity), but two impurities were observed by ¹H NMR and LC/MS and the product failed elemental analysis. LC/MS showed the impurities to be present at ca. 5% each. The impurities appeared to be the two regioisomers (each a mixture of two diastereomers) generated from the addition of dibenzoylmethane to the styrene dimer ((PhCO)₂CHCH(Ph)CH₂CH(Ph)Me and (PhCO)₂CHCH(CH₂Ph)CH(Ph)Me): C₃₁H₂₈O₂ requires *m/z* 432, M+Na = 455 observed.

13. The submitters recrystallized a sample from 10:1 hexanes-CH₂Cl₂ for elemental analysis and melting point.

14. IR (thin film): ν_{\max} 3062, 3028, 2968, 1693, 1662, 1595, 1579, 1494, 1447, 1321, 1264, 1215, 1194, 1180, 979, 907, 756, 732, 686 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ : 1.34 (d, *J* = 7.0 Hz, 3 H), 4.07 (dq, *J* = 10.0, 7.0 Hz, 1 H), 5.60 (d, *J* = 10.0 Hz, 1 H), 7.05–7.57 (m, 11 H), 7.73 (d, *J* = 7.5 Hz, 2 H), 8.03 (d, *J* = 7.5 Hz, 2 H); ¹³C NMR (CDCl₃, 100 MHz) δ : 20.1, 41.1, 64.4, 126.5, 127.6, 128.3, 128.3, 128.6, 128.7, 132.9, 133.4, 136.7, 137.0, 143.6, 194.5, 194.8. mp 123–124 °C (lit. 126–127 °C).² Anal. Calcd for C₂₃H₂₀O₂: C, 84.12; H, 6.14; Found: C, 84.10; H, 6.06.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

As one of the most common methodologies for the formation of carbon-carbon bonds, the alkylation of 1,3-dicarbonyl compounds usually requires the use of a stoichiometric amount of base and an organic halide. An alternative reaction via transition metal-catalyzed addition of 1,3-dicarbonyl compounds to alkenes would provide a more atom-economical approach and has attracted much interest in recent years.

Recently, Widenhoefer and co-workers reported an elegant intramolecular hydroalkylation of alkenes by carbonyl compounds catalyzed by palladium.³ Compared with intramolecular addition, intermolecular hydroalkylations of alkenes involving such activated methylene C-H bonds were rarely reported. Widenhoefer reported a platinum- or palladium-catalyzed intermolecular addition of ethylene with β -diketones.⁴ Hartwig also reported a palladium-catalyzed addition of mono- and dicarbonyl compounds to conjugated dienes.⁵

Using the addition of 2,4-pentanedione to styrene as a prototype, we found:⁶ (1) AgOTf or AuCl₃ provided only trace amounts of the desired product, (2) the combination of AuCl₃ and AgOTf provided the desired product in good yields, (3) changing the counter ion of the silver salt from OTf lowered the yield, but no difference was observed when the counter ion of gold was changed, and (4) CH₂Cl₂ was the solvent of choice relative to DCE and nitromethane. It should be noted that since the catalytic system is very strongly Lewis acidic, THF was not stable in the solution of the gold/silver catalyst. THF decomposed almost immediately, and a semi-solid was obtained in the tube.

A side reaction observed in this system was the polymerization of styrene, in which the dimerization promoted by metal triflate species was found to be the main reaction and gave 1,3-diphenyl-but-1-ene as the main by-product.⁷ Since styrene readily dimerized in the reaction, the use of catalytic AuCl₃/AgOTf in CH₂Cl₂ with an excess of styrene, which was diluted and slowly added to the reaction, provided the best yield. It should be mentioned that dimerization became more serious with an increase in the reaction scale, especially for the less reactive 1,3-diketone substrates, such as 2,4-pentanedione. In these cases, increasing the excess of styrene and reaction temperature was beneficial. Alternatively, use of a more diluted solution and slower addition helped to inhibit the dimerization of styrene. The results of various 1,3-diketones and styrenes are summarized in Table 1.

Since gold(III) chloride is expensive, decreasing the amount of catalyst was also attempted. For the less active diketones, such as 2,4-pentandione, reduction of the amount of gold(III) resulted in a decrease in yield. However, for the procedure described above, there was only ca. 3% decrease in yield.

This reaction was reversible at higher temperatures when catalyzed by gold or silver catalyst.⁸ Dibenzoylmethane derivatives were most prone to the reverse reaction, which gave the diketone and the styrene dimer. In small scale reactions (1 mmol or less), the reversibility was not a serious problem, since it was not necessary to remove CH₂Cl₂ before separation. However, for larger scale reactions, the catalyst had to be removed by a short silica gel column before concentration, especially for the dibenzoylmethane derivatives (although it was not necessary for the 2,4-pentanedione derivatives).

Under the same reaction conditions, various cyclic dienes and cyclic enol ethers were reacted with dibenzoylmethane and 1-benzoylacetone (Table 2).⁹ Addition to a triene (entry 2) was also selective in the generation of a diene product. The reaction had to be carried out at low temperature in some cases in order to prevent polymerization or dimerization of the diene (entries 3 and 4). The use of cyclic alkenes bearing a heteroatom (entries 5-8) resulted in selective product formation. However, addition of dibenzoylmethane to an ether-substituted DHP (entries 6 and 7) led to a significant amount of bis-alkylation products. The use of simple cyclic and acyclic alkenes led to very low conversions, while use of acyclic conjugated dienes resulted in the formation of a complicated unidentified mixture. The use of sterically hindered dienes or less activated methylenes (such as 2,4-pentadione and cyclic diketones) also led to low conversions under the present conditions.

Table 1 Addition of β -Diketone to Alkenes Catalyzed by Gold Catalyst^a

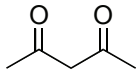
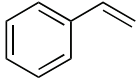
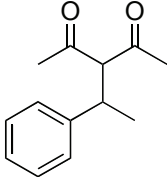
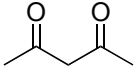
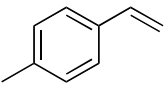
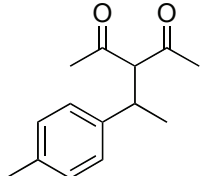
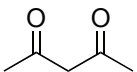
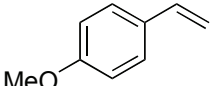
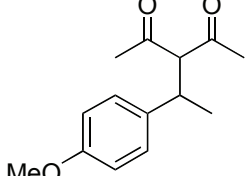
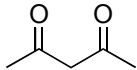
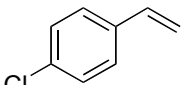
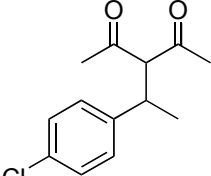
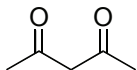
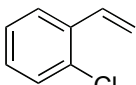
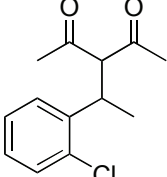
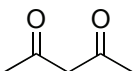
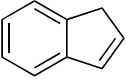
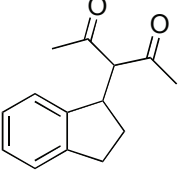
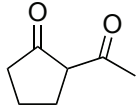
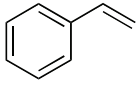
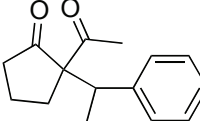
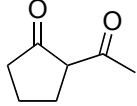
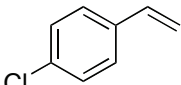
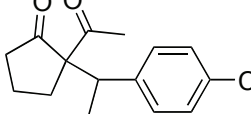
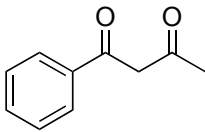
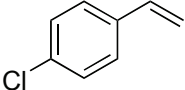
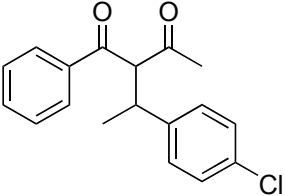
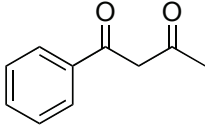
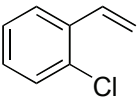
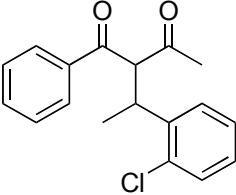
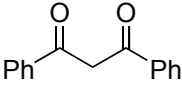
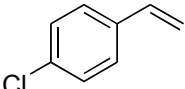
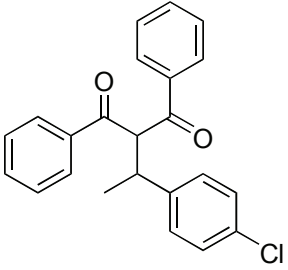
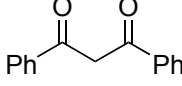
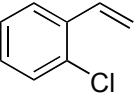
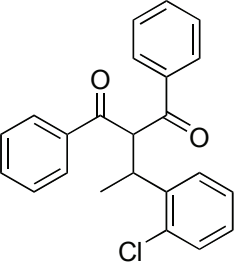
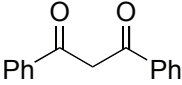
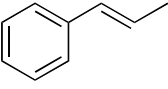
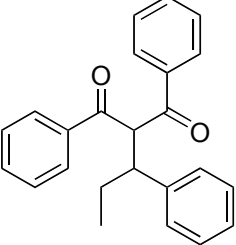
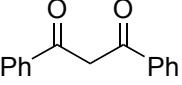

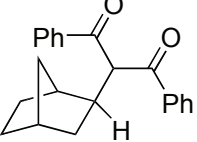
Entry	β -Diketone	Alkenes ^b	Product	Yield (%) ^c
1				89 ^d
2				94
3				62
4				97
5 ^e				50
6				44
7				70 (1:1) ^f
8				55 (1:1) ^f

Table 1 (continued)

Entry	β -Diketone	Alkenes ^b	Product	Yield (%) ^c
9				89 (1:1) ^f
10				67 (1:1) ^f
11				98
12				91
13				39 ^g
14				81

^a Reaction conditions: 1 mmol scale in dichloromethane. ^b The alkenes (1.5 equiv., diluted to 3 mL) were added by syringe pump over 5 h. ^c Isolated yield. ^d This reaction was also carried out on a 30 mmol scale (2 equiv. of styrene was used), and 70–74% yields were achieved. ^e The reaction was carried out in refluxing nitromethane. ^f The ratio of two diastereomers was determined by ¹H-NMR. ^g Approximately 56% of the diketone was recovered.

Table 2 Addition of β -diketone to cyclic alkenes catalyzed by gold catalyst^a

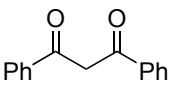

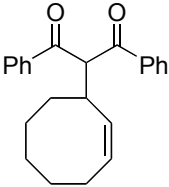
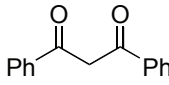

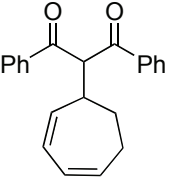
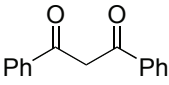

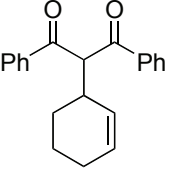
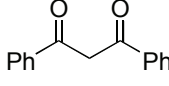

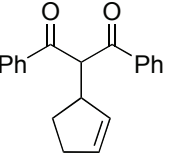
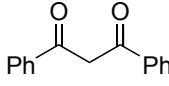

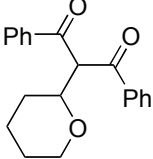
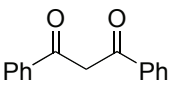
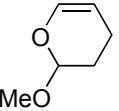
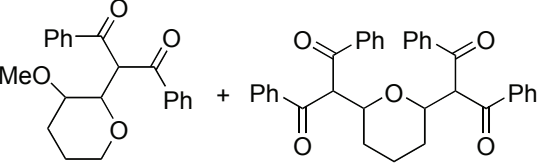
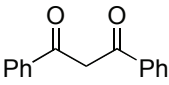
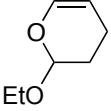
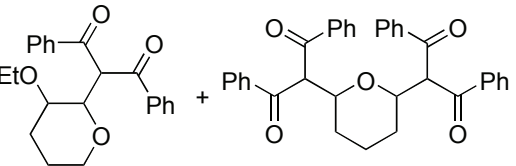
Entry	β -Diketone	Alkenes ^b	Product	Yield (%) ^c
1				65
2 ^d				42
3 ^e				51
4 ^e				50
5 ^e				68
6				47 15
7				44 15

Table 2 (continued)

Entry	β -Diketone	Alkenes ^b	Product	Yield (%) ^c
8				58
9				38 (1.4:1) ^f
10				35 (1.2:1) ^f

^a Reactions were performed in dry dichloromethane. ^b Alkenes were added by syringe pump. ^c Isolated yield. ^d The position of the double bonds was confirmed by COSY-NMR. ^e Reactions were run at 0 °C. ^f The ratio of the two diastereoisomers was determined by ¹H NMR.

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Dibenzoylmethane: 1,3-Propanedione, 1,3-diphenyl-: (120-46-7)

Styrene: Benzene, ethenyl-: (100-42-5)

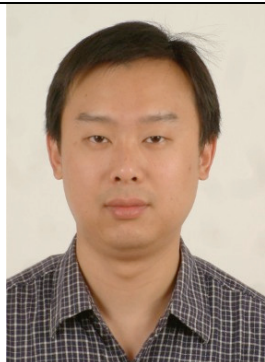
Gold(III) chloride; (13453-07-1)

Silver trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, silver(1+) salt; (2923-28-6)

1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione: 1,3-Propanedione, 1,3-diphenyl-2-(1-phenylethyl)-; (116140-58-0)



Chao-Jun Li (born in 1963) received his BS at Zhengzhou University, MS at the Chinese Academy of Sciences in Beijing and Ph.D at McGill University in 1992, with T. H. Chan and D. N. Harpp. He spent 1992-94 as a NSERC Postdoctoral Fellow with B. M. Trost at Stanford University. He was an Assistant Professor (1994), Associate Professor (1998) and Full Professor (2000-2003) at Tulane University, and a visiting faculty (with Robert G. Bergman) at University of California at Berkeley (2002). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts focus on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and possess high “atom-efficiency”.

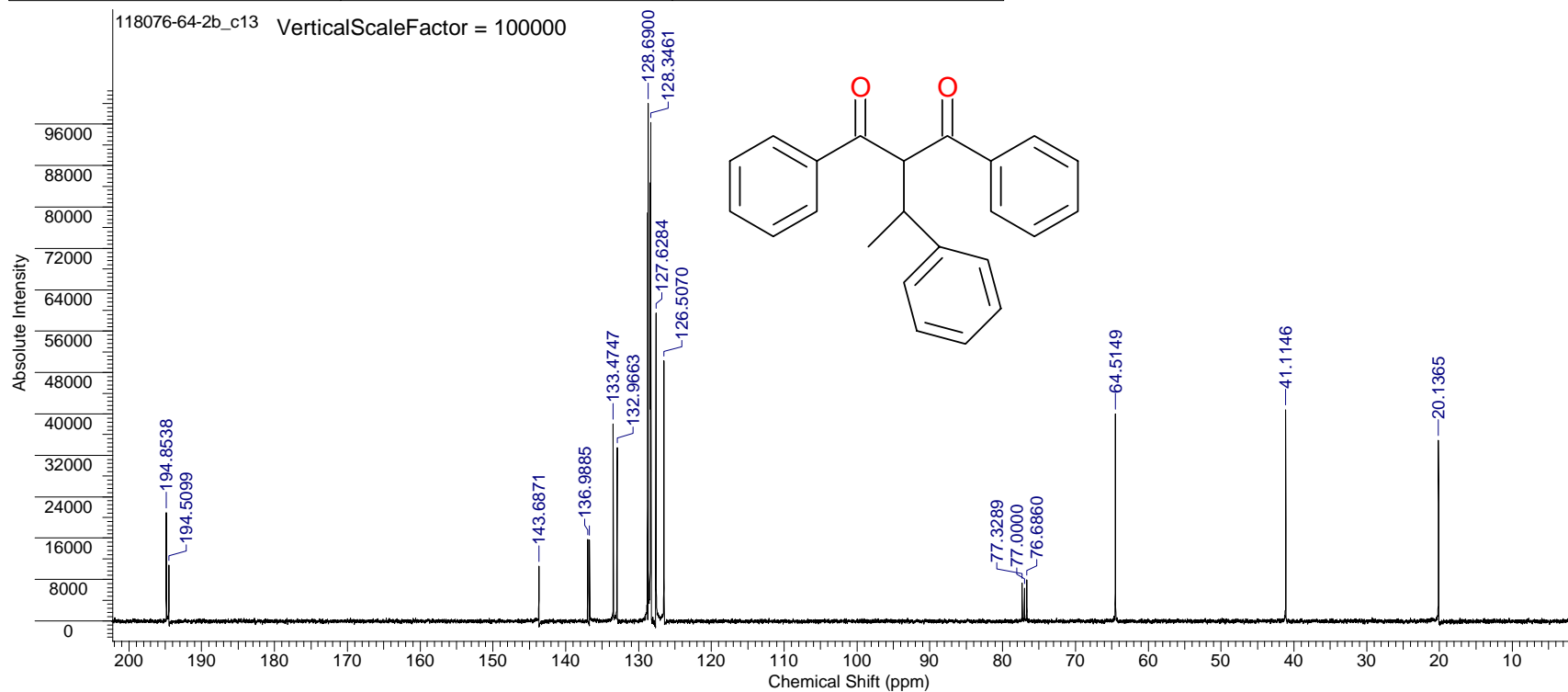


Xiaoquan Yao was born in 1973 in Nanjing, China. He received his B.Sc. at Nanjing Normal University in 1995, and his Ph.D. at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences in 2000 with Prof. Huilin Chen. He spent 2001-2002 as a postdoctoral fellow in Prof. Xiyan Lu's laboratory at Shanghai Institution of Organic Chemistry, CAS and then another postdoctoral stint at McGill University in Canada with Prof. Chao-Jun Li (2003-2006). He is currently working as a faculty member at Nanjing University of Aeronautics & Astronautics in China. His current research interests are focused on metal-mediated C-C bond formation reactions in water and organic materials.



Brian Jones was born in 1975 in Warwick, Rhode Island. He received his B.S. and M.S. degrees from Worcester Polytechnic Institute in 1997 and 1998 respectively. While in school, he worked as a Co-op student in the Medicinal Chemistry department at Pfizer in Groton, CT. Upon graduation he joined the Pfizer Chemical Research and Development group where he currently works as a process chemist.

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