# Enantioselective Conjugate Addition of Diethylzinc to Enones with Chiral Copper-QUIPHOS Catalyst
## Influence of the Addition of Water on the Enantioselectivity

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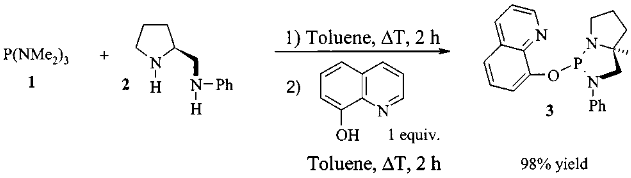
**Keywords:** Enones / Asymmetric synthesis / 1,4-Addition / Copper / Diethylzinc / P ligands / N Ligands / QUIPHOS

The use of a new chiral copper catalyst involving QUIPHOS as ligand in the 1,4-addition of $Et_2Zn$ to enones is reported. The dramatic beneficial effect of addition of water or $Zn(OH)_2$ to this system has been investigated, and led to an improvement of the enantiomeric excess from 7 to 61% *ee*.

## Introduction

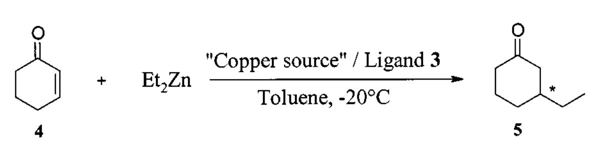
Organometallic chemistry has become a cornerstone of modern organic synthesis, and today hardly any total syntheses are envisioned without a key step involving some nucleophilic organometallic reagents.[1] In this area, asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated compounds has appeared as a powerful tool for carbon−carbon bond formation with simultaneous introduction of a new stereogenic center at the β-position.[1,2] In the majority of these reactions, the carbon nucleophile is an ionic species, and most often an organocopper reagent. Although stoichiometric processes have been widely described,[3] few highly enantioselective catalytic versions of the conjugate addition of organometallic reagents to enones have been reported to date. Alexakis et al. were the first to report enantioselective addition of diethylzinc to cyclohexenone in the presence of a catalytic amount of a chiral copper−phosphane complex.[4] Since this pioneering work, numerous copper catalysts, with a wide variety of chiral phosphorus ligands were found to be efficient in the asymmetric conjugate addition of organozinc reagents to cyclic enones.[5] However, at present no one ligand system affords a copper catalyst showing uniformly superb selectivity against a wide range of substrate variables (e.g. cyclic vs. acyclic enones, or cyclic enones with different ring sizes). Recently, BINOL based enantiopure phosphoramidite-copper complexes have been found by Feringa et al.[6] to catalyze the 1,4-addition of diorganozincs to both cyclic and acyclic α,β-unsaturated ketones with remarkable enantioselectivities. On the other hand, Pfaltz et al.[7] have reported other similarly efficient organophosphorus ligands based on a chiral BINOL moiety. In the context of our studies, we have recently described the straightforward synthesis of a new class of chiral P-pyridine and P-quinoline phosphane ligands,[8] and their successful use in asymmetric palladium catalyzed allylic substitution[9] and copper(II) catalyzed Diels−Alder reactions[10] leading to enantiomeric excesses (*ee*) of up to 96%. In this paper, we report our investigations dealing with the use of such ligands in an enantioselective copper catalyzed 1,4-addition of diorganozinc to various enones.

Due to its stability to air and moisture, one of these ligands, (2*R*,5*S*)-2-(8-quinolinoxy)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **3** (QUIPHOS), has particularly focused our attention. Thus, its synthesis was easily accomplished by an exchange reaction between tris(dimethylamino)phosphane **1** and (*S*)-2-anilinomethylpyrrolidine **2** in refluxing toluene, followed by addition of one equivalent of hydroxyquinoline[8] (Scheme 1).



Scheme 1. Synthesis of ligand QUIPHOS

Using cyclohexenone **4** as a test substrate, an asymmetric conjugate addition of diethylzinc was carried out in toluene at −20 °C with numerous copper-QUIPHOS **3** complex catalysts (ratio Cu/**3** = 1:2) (Scheme 2).



Scheme 2. Asymmetric addition of $Et_2Zn$ to cyclohexenone **4**

Although chemical yields up to 82% have been obtained in all cases where the reaction was performed in toluene, it clearly appears that the nature of the copper source used has an important influence on the outcome of the reaction

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Table 1. Influence of the nature of the copper source on the enantioselectivity

| Entry[a] | Copper source | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 69 | 22 (*R*) |
| 2 | Cu(OTf) | 72 | 2 (*S*) |
| **3** | **CuI** | **53** | **45 (*R*)** |
| 4 | CuBr | 82 | 24 (*R*) |
| 5 | CuCl | 85 | 8 (*R*) |
| 6 | CuI + AgOTf | 58 | 25 (*R*) |

[a] Reaction performed at −20°C in toluene for 12 h, 0.5 mol% of CuX, 1 mol% of **3** and **2** equiv. of $Et_2Zn$ with respect to 4. – [b] Isolated yield. – [c] Enantiomeric excess of **5** determined by $^{13}C$ NMR analysis after synthesis of the diastereomeric aminals by reaction with optically pure (*S,S*)-1,2-diphenylethylenediamine (ref. [11]).

in terms of enantioselectivity, which varied from 2 to 45% ee[11] (Table 1).

Thus, employing CuI as copper source, the expected product was obtained in 53% yield and 45% *ee* (Table 1, entry 3), whereas the most used $Cu(OTf)_2$ and Cu(OTf) complexes led to lower enantiomeric excesses (Table 1, entries 1 and 2, 22 and 2% ee, respectively). The effects on the enantioselectivity of several other variables, such as the nature of the solvent, the temperature of the reaction, and the amount of ligand involved were also investigated (Table 2).

## Experimental Conditions

A dramatic solvent effect controls the enantioselectivity of the reaction (Table 2, entries 1−5). Although similar yields are obtained in all cases, enantiomeric excesses varying from 6 to 63% *ee* were encountered. Moreover, a spectacular variation of the enantiomeric excess was noticed when 0.5 equivalent of water (with respect to the substrate) was added.[12] Thus, performing the reaction in dichloromethane led to an increase of the enantioselectivity from 7 to 61% *ee* (Table 2, entries 3 and 8), whereas a significant decrease from 45 to 6% *ee* was observed in toluene (Table 2, entries 1 and 6). The present catalytic system could not be used at temperatures below −20 °C and over 40 °C due to a lack of catalyst activity (Table 2, entries 9 and 10). Furthermore, attempts to improve the catalyst activity by varying the metal/ligand ratio from 1:1 to 1:10 did not enhance the enantioselectivity of the reaction (Table 2, entries 13 and 14, 2 and 63% *ee*, respectively). Moreover, a decrease or an increase of the amount of the catalyst did not lead to an improvement of the enantiomeric excess (Table 2, entries 15 and 16, 44 and 5% *ee*, respectively).

In order to rationalize the role of water in this catalytic system, numerous experiments were conduced. Addition of increasing amounts of water led to spectacular variations in terms of enantioselectivity, whereas no significant variation in the obtained chemical yields was noticed (Figure 1). The best result was obtained using $Cu/3/H_2O/Et_2Zn$ in a 0.005:0.01:0.5:2 molar ratio, with respect to the substrate, leading to the expected product in 61% *ee*. It is noteworthy

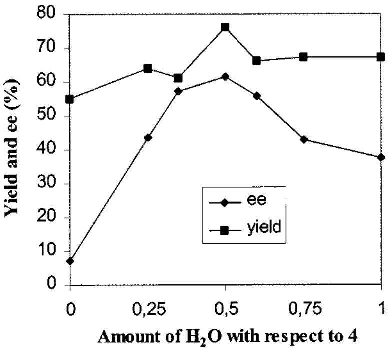


Figure 1. Influence of the amount of $H_2O$ on the yield and the enantiomeric excess

Table 2. Asymmetric addition of $Et_2Zn$ to cyclohexenone **4** under various conditions, in the copper catalyzed 1,4-addition of $Et_2Zn$ to **4**

| Entry[a] | Solvent | Additive[b] | Ratio Cu/**3** | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|---|
| 1 | Toluene | – | 1:2 | 53 | 45 (*R*) |
| 2 | THF | – | 1:2 | 53 | 25 (*R*) |
| 3 | $CH_2Cl_2$ | – | 1:2 | 55 | 7 (*R*) |
| 4 | 1,2-Dichloroethane | – | 1:2 | 69 | 30 (*R*) |
| 5 | $CCl_4$ | – | 1:2 | 34 | 7 (*R*) |
| 6 | Toluene | $H_2O$ | 1:2 | 55 | 6 (*R*) |
| 7 | THF | $H_2O$ | 1:2 | 50 | 22 (*R*) |
| **8** | **$CH_2Cl_2$** | **$H_2O$** | **1:2** | **76** | **61 (*R*)** |
| 9[e] | $CH_2Cl_2$ | $H_2O$ | 1:2 | – | – |
| 10[f] | $CH_2Cl_2$ | $H_2O$ | 1:2 | 27 | 44 (*R*) |
| 11 | 1,2-Dichloroethane | $H_2O$ | 1:2 | 55 | 23 (*R*) |
| 12 | Hexane | $H_2O$ | 1:2 | – | – |
| 13 | $CH_2Cl_2$ | $H_2O$ | 1:1 | 46 | 2 (*R*) |
| 14 | $CH_2Cl_2$ | $H_2O$ | 1:10 | 53 | 63 (*R*) |
| 15[g] | $CH_2Cl_2$ | $H_2O$ | 1:2 | 78 | 44 (*R*) |
| 16[h] | $CH_2Cl_2$ | $H_2O$ | 1:2 | 15[i] | 5 (*R*) |

[a] Reaction performed at −20°C using 0.5 mol% of CuI and 1 mol% of **3** with respect to **4** for 12 h unless otherwise noted. – [b] Reaction performed using 0.5 equiv. of water with respect to the substrate. – [c] Isolated yield. – [d] Enantiomeric excess of **5** determined by $^{13}C$-NMR analysis after synthesis of the diastereomeric aminals by reaction with optically pure (*S,S*)-1,2-diphenylethylenediamine (ref.[11]). – [e] Reaction performed at −40°C for 72 h. – [f] Reaction performed at 20°C for 1.5 h. – [g] Reaction performed at −20°C using 5 mol% of CuI. – [h] Reaction performed at −20°C using 0.05 mol% of CuI. – [i] Numerous non-identified products have been observed under these experimental conditions.

that addition of more than one equivalent of water led to a dramatic decrease of the enantioselectivity and chemical yield.

The influence of water on the outcome of the reaction is surprising, and a possible explanation could be the in situ formation of $Zn(OH)_2$ species, which could act as a Lewis acid by complexation to the enone carbonyl, thereby increasing the enantiofacial differentiation, and enhancing the enantioselectivity of the reaction (Table 3).

Table 3. Influence of the nature of numerous additives on the enantioselectivity in the copper catalyzed 1,4-addition of $Et_2Zn$ to **4**

| Entry[a] | Additive | Amount of additive with respect to **4** | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|
| 1 | $Zn(OH)_2$ | 0.1 equiv. | 64 | 44 (*R*) |
| **2** | **$Zn(OH)_2$** | **0.25 equiv.** | **81** | **53 (*R*)** |
| 3 | $Zn(OH)_2$ | 0.5 equiv. | 53 | 16 (*R*) |
| 4 | $ZnCl_2$ | 0.25 equiv. | 82 | 9 (*R*) |
| 5 | Al(O*i*-Pr)$_3$ | 0.25 equiv. | 31 | 17 (*R*) |
| 6 | Ti(O*i*-Pr)$_4$ | 0.25 equiv. | 39 | 1 (*R*) |

[a] Reaction performed at −20 °C in $CH_2Cl_2$ for 12 h with 0.5 mol-% of CuI and 1 mol-% of **3** with respect to **4**. – [b] Isolated yield. – [c] Enantiomeric excess of **5** determined by $^{13}C$ NMR analysis after synthesis of the diastereomeric aminals by reaction with optically pure (*S,S*)-1,2-diphenylethylenediamine (ref. [11]).

Replacement of water by $Zn(OH)_2$ under the best experimental conditions, led to the same results in terms of yield and enantioselectivity (Table 3, entry 2, 81% yield and 53% *ee*). In a similar way, a decrease or an increase of the amount of $Zn(OH)_2$ involved in this reaction did not improved the enantiomeric excess (Table 3, entries 1 and 3, 44 and 16%, respectively).

Recently, nonlinear effects (NLE) have been postulated to act as a probe to obtain information on the subtle mechanisms by which the enantioselectivity is generated. In this area, Pfaltz et al. were the first to report a (−)-NLE in the addition of isopropylcuprate to cycloheptenone.[13] In order to substantiate this assumption in our catalytic system, we made use of nonlinear effects to identify a higher order molecularity of the catalyst (Figure 2).

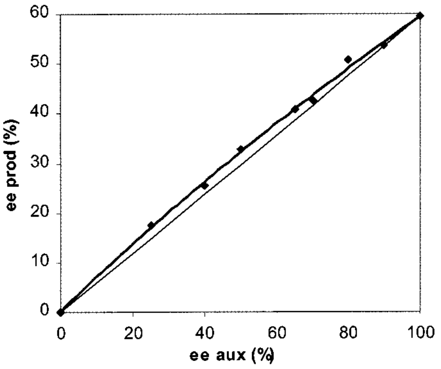
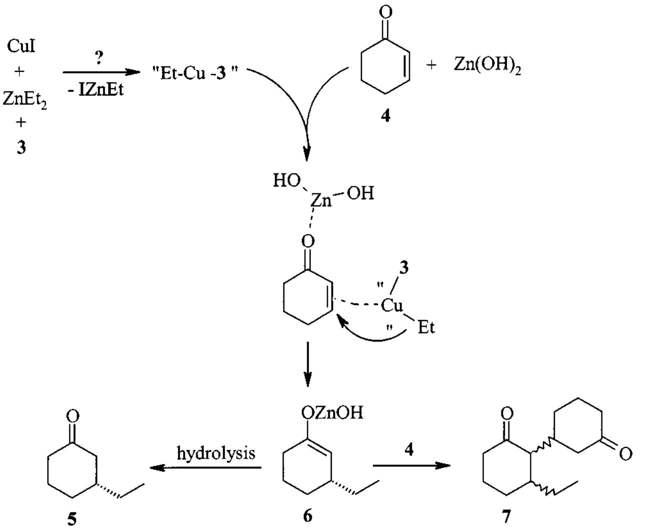


Figure 2. NLE observed in the copper catalyzed 1,4-addition of $Et_2Zn$ to **4**

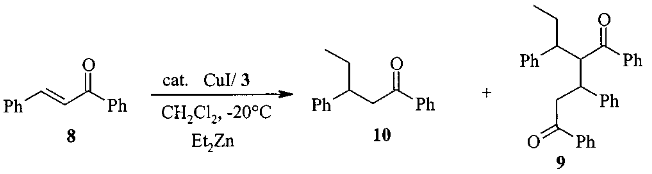
The results obtained clearly demonstrate a slight, positive, nonlinear effect. No explanation can be given to date for this NLE, even if we can suggest that the aggregation of cuprates, which is usually more complex than with other organometallic reagents, is responsible for this effect.[14]

On the basis of all these observations, a possible pathway for the 1,4-addition of $Et_2Zn$ to cyclohexenone could be proposed involving the complexation of a molecule of $Zn(OH)_2$ to the enone carbonyl, followed by complexation of the copper alkyl species (generated from the reaction of $Et_2Zn$ with the copper complex) to the double bond of the enone. Alkyl transfer to the β-position of the enone could generate enolate **6**, which upon protonation provides ethylcyclohexanone **5** (Scheme 3).[15]



Scheme 3. Postulated pathway for the copper catalyzed 1,4-addition of $Et_2Zn$ to **4**

As a proof of the generation of this zinc enolate **6**, compound **7**, resulting from the capture of **6** by another molecule of cyclohexenone, has been isolated and clearly identified by NMR spectroscopic analysis. On the other hand, similar results have been encountered when performing the reaction with chalcone **8** instead of cyclohexenone (Scheme 4).



Scheme 4. Asymmetric addition of $Et_2Zn$ to chalcone **8**

In this case, adduct **9** has been isolated and fully characterized by its X-ray structure analysis (Figure 3).[16]

The optimal catalytic system was finally applied to other enone substrates, performing the reaction in the presence or absence of water and $Zn(OH)_2$ and $Et_2Zn$ or $Bu_2Zn$ as organometallic reagents (Table 4).

In all cases, a total conversion of the substrate and a significant effect of addition of $Zn(OH)_2$ on the enantioselectivity was noticed. Nevertheless, although reasonably good yields were found using cyclic enones, low yields varying from 4 to 20% were encountered with acyclic enones. This

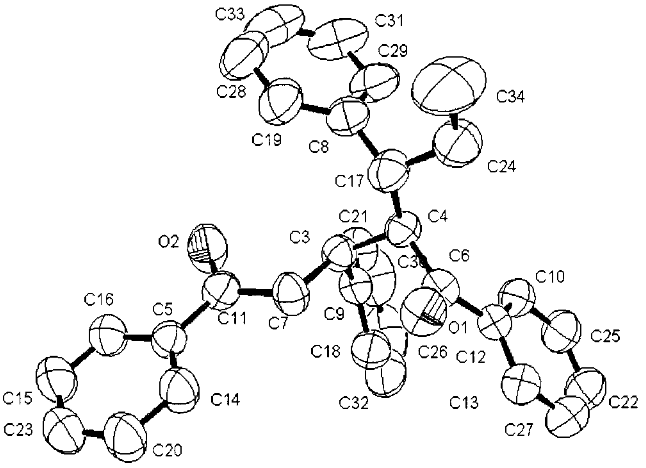
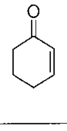
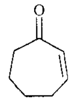
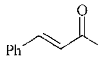
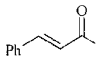


Figure 3. X−ray structure of **9**, showing labeling scheme. Selected bond lengths [Å]: O1−C6, 1.224(2), O2−C11, 1.217(2), C17−C24, 1.524(2), C3−C4, 1.560(2), C3−C9, 1.514(2), C7−C11, 1.508(2), C5−C11, 1.491(2). Selected bond angles [°]: C7−C4−C3, 113.9(1), C4−C3−C9, 111.7(1), C3−C4−C6, 110.8(1), C5−O2−C11, 119.5(2), C7−C11−O2, 120.6(1), O1−C6−C4, 119.4(1), O1−C12−C6, 119.3(1)

Table 4. Asymmetric catalyzed addition of $Et_2Zn$ and $n Bu_2Zn$ to different enones under various experimental conditions

| Entry | Enone | Organometallic reagent | Additive | Yield (%)[f] | ee (%) |
|---|---|---|---|---|---|
| 1[g] |  **4** | $Et_2Zn$[a] | - | 55 | 7 |
| | | | $H_2O$[d] | 76 | 61 |
| | | | $Zn(OH)_2$[e] | 81 | 53 |
| | | $Bu_2Zn$[a] | - | 65 | 30 |
| | | | $H_2O$[d] | 42 | 14 |
| | | | $Zn(OH)_2$[e] | 42 | 17 |
| 2[g] |  **11** | $Et_2Zn$[a] | - | 82 | 22 |
| | | | $H_2O$[d] | 71 | 37 |
| | | | $Zn(OH)_2$[e] | 48 | 35 |
| | | $Bu_2Zn$[a] | - | 64 | 2 |
| | | | $H_2O$[d] | 34 | 7 |
| | | | $Zn(OH)_2$[e] | 57 | 13 |
| 3[h] |  **8** | $Et_2Zn$[a] | - | 19 | 15 |
| | | | $H_2O$[d] | 13 | 22 |
| | | | $Zn(OH)_2$[e] | 10 | 44 |
| | | $Bu_2Zn$[b] | - | 6 | 2 |
| | | | $H_2O$[d] | 4 | 0 |
| | | | $Zn(OH)_2$[e] | 20 | 5 |
| 4[h] |  **12** | $Et_2Zn$[c] | - | 7 | 14 |
| | | | $H_2O$[d] | 16 | 15 |
| | | | $Zn(OH)_2$[e] | 18 | 49 |
| | | $Bu_2Zn$[b] | - | 10 | 0 |
| | | | $H_2O$[d] | 9 | 0 |
| | | | $Zn(OH)_2$[e] | 7 | 4 |

[a] Reaction performed at −20 °C for 12 h with 0.5 mol-% of CuI and 1 mol-% of **3** with respect to the substrate unless otherwise noted. − [b] Reaction performed at room temp. for 12 h with 0.5 mol-% of CuI and 1 mol-% of **3** with respect to the substrate. − [c] Reaction performed at room temp. for 24 h with 0.5 mol-% of CuI and 1 mol-% of **3** with respect to the substrate. − [d] 0.5 equiv. with respect to the substrate. − [e] 0.25 equiv. with respect to the substrate. − [f] Isolated yield. − [g] Enantiomeric excess determined by $^{13}C$ NMR analysis after synthesis of the diastereomeric aminals by reaction with optically pure (*S,S*)-1,2-diphenylethylene diamine (ref. [11]). − [h] Enantiomeric excess determined by HPLC analysis on a Daicel Chiralcel OD-H column.

was due to the formation of numerous unidentified byproducts (Table 4, entries 3 and 4). Moreover, an improvement in the enantiomeric excess from 7 to 53% *ee* was found by addition of $Zn(OH)_2$. Furthermore, whatever the considered substrate, the use of $n Bu_2Zn$ instead of $Et_2Zn$ led to low enantioselectivities (up to 22%) (Table 4, entry 1).

In conclusion, we have described the use of a new chiral copper catalyst involving QUIPHOS as ligand in the 1,4-addition of $Et_2Zn$ to enones. The dramatic beneficial effect of addition of water or $Zn(OH)_2$ to this system has been investigated, leading to an improvement of the enantiomeric excess from 7 to 61% *ee* in the enantioselective 1,4-addition of $Et_2Zn$ to cyclohexenone. Additional studies concerning the mechanism, and more precisely the role of water and $Zn(OH)_2$, are currently in progress.

## Experimental Section

All solvents were purified according to reported procedures, and reagents were used as commercially available. Ethyl acetate and petroleum ether (35−60 °C) were purchased from SDS and used without any further purification. Column chromatography was performed on SDS silica gel (70−230 mesh). $^1H$-NMR and $^{13}C$-NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer, working at 200.00 MHz and 50.16 MHz, respectively (the usual abbreviations are used: s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet). Tetramethylsilane was used as an internal standard. All chemical shifts are given in ppm.

**General Procedure:** A solution of CuI (1.0 mg, 5.2 μmol) and QUIPHOS (3.6 mg, 10.4 μmol) in dry $CH_2Cl_2$ was stirred for 45 min at room temperature under argon. To this solution was added $H_2O$ (9.4 μL, 0.52 mmol) or $Zn(OH)_2$ (25.8 mg, 0.26 mmol). The mixture was stirred for 45 min at room temperature under argon, then cooled at the indicated temperature. $Et_2Zn$ (1.0 M in hexanes, 2.1 mL) or $Bu_2Zn$ (1.0 M in heptane, 2.1 mL) and enone (1.04 mmol) were added. After stirring for the indicated period, a 5 N HCl solution (2 mL) was added and the mixture was extracted with $Et_2O$ (3× 10 mL). The organic phase was dried with $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (petroleum ether/ethyl acetate, 8:1 for cyclic enones or 12:1 for acyclic enones).

**6-Ethylbicyclohexyl-2,3′-dione (7):** Colorless oil. IR (neat): $\tilde{\nu}$ = 2973−2872 (C−H str Al), 1720, 1700 (2 CO str). − $^1H$ NMR ($CDCl_3$) (mixture of isomers): δ = 2.5−2.4 (m, 1 H, CHCO), 2.4−2.0 (m, 6 H, 3 $CH_2CO$), 1.9−1.2 (m, 12 H, 5 $CH_2$ and 2 CH), 0.75−0.95 (m, 3 H, $CH_3$). − $^{13}C$ NMR ($CDCl_3$) (mixture of isomers): δ = 212.0, 211.8, 211.2 (3 CO), 60.4, 60.3 (2 CHCO), 46.2, 44.7, 44.2, 43.4, 41.7, 41.4, 41.0 (7 $CH_2CO$), 34.4, 38.1 (2 $CHCH_2$), 31.1, 29.6, 27.4, 26.2, 25.5, 25.4, 23.5, 23.3 (8 $CH_2CH_2$), 11.5, 11.1 (2 $CH_3$).

**1,3,5-Triphenyl-2-(1-phenylpropyl)pentane-1,5-dione (9):** White solid, m.p. 140 °C. − IR (KBr): $\tilde{\nu}$ = 3073−3035 (C−H str Ar), 2968−2929 (C−H str Al), 1688, 1674 (2 CO str). − $^1H$ NMR ($CDCl_3$) (mixture of isomers): δ = 7.9−6.9 (m, 20 H, ArH), 4.6−4.3 (m, 1 H, CHCO), 4.0−3.0 (m, 4 H, $CH_2CO$ and 2 CH), 1.8−1.5 (m, 2 H, $CH_2CH_3$), 0.8−0.5 (m, 3 H, $CH_3$). − $^{13}C$ NMR ($CDCl_3$) (mixture of isomers): δ = 204.3, 203.2, 198.3, 197.9 (4 CO), 142.0, 141.9, 141.7, 140.9, 139.6, 139.0, 136.7, 136.6 (8 $C^{IV}$ Ar), 132.6, 132.4, 132.3, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.5, 127.3, 126.6, 126.3, 126.0 (17 CH Ar), 56.8, 54.0 (2 CHCO), 48.8, 48.4 (2 CH), 41.6, 41.5 (2 CH), 38.3 (1 $CH_2CO$), 26.8, 26.2 (2 $CH_2CH_3$), 11.7, 11.6 (2 $CH_3$).

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[16] X-ray analysis of **9**: A thin white plate monocrystal of $C_{32}H_{30}O_2$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.4×0.3×0.3 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Mo-*Kα* radiation. Cell constants and the orientation matrix for data collection were obtained from a least square refinement using setting angles of 30 reflections in the range $\theta = 1-26.3°$, which corresponded to a monoclinic cell with dimensions: $a = 11.1165(8)$, $b = 22.6640(10)$, $c = 11.0720(5)$ Å. For $Z = 4$ and $M = 446.59$, $\rho_{calcd} = 1.119$ g cm$^{-3}$. The space group was determined to be $P2_1/c$ from the systemic absences. A total of 9651 reflections were collected at $T = 298$ K. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 142335. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44(1223)336–033, E-mail: deposit@ccdc.cam.ac.uk].

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