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Conformational Consequences of the Dynamic Processes in the Stereolabile Atropisomers of Acyl-Substituted *m*-Terphenyl Derivatives

Lodovico Lunazzi, Andrea Mazzanti,* and Mirko Minzoni[1]

Department of Organic Chemistry "A. Mangini", University of Bologna, Viale Risorgimento 4, Bologna 40136, Italy

mazzand@ms.fci.unibo.it

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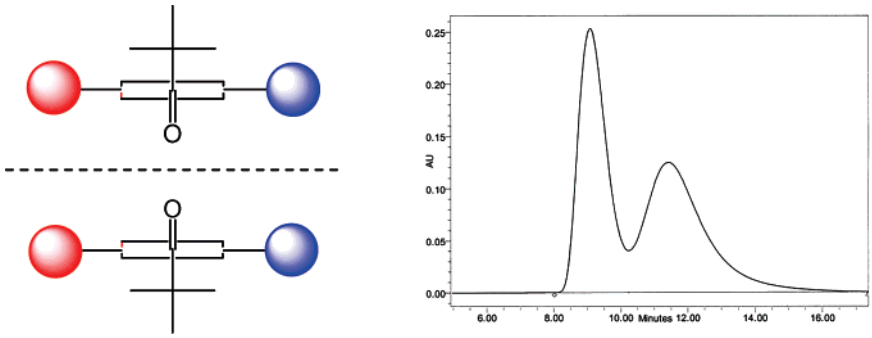

By means of low-temperature NMR spectroscopy, conformers (stereolabile atropisomers) due to the restricted rotation about the Ar−Ar and Ar−C(O)R bonds were detected in a number of acylphenyl derivatives, substituted in positions 2 and 6 by the 3-isopropylphenyl moiety (compounds **1**−**3**, R = H, Me, and *t*-Bu, respectively). The conformational assignment was accomplished on the basis of the symmetry of the low-temperature ^{13}C NMR spectra with the added support of ab initio calculations. The interconversion barriers were also determined by complete line shape simulation of the NMR spectra, and the experimental values were satisfactorily reproduced by ab initio calculations. In the case of the asymmetric derivative **4**, two enantiomers, generated by the restricted *t*-BuC(O)−Ar rotation, were found sufficiently stable to allow their separation by means of the enantioselective HPLC technique at ambient temperature and to obtain the corresponding CD spectra.

Introduction

It has been recently reported[2] that *p*-terphenyl derivatives bearing equal substituents in the ortho positions of the two external rings give rise to cis and trans stereolabile diastereoisomers (atropisomers) that could be detected by low-temperature NMR spectroscopy. This suggests that analogously substituted *m*-terphenyl compounds bearing, in addition, an acyl group on the central phenyl ring should originate an even greater number of this type of atropisomers that would be amenable to NMR detection. In the case of a particularly crowded derivative, it should also be possible, in principle, to achieve a physical separation of the two enantiomeric forms. Compounds **1**−**4** (Chart 1) were accordingly synthesized for this purpose: the isopropyl moiety was introduced to take advantage of the diastereotopicity of its methyl groups under the mode of slow rotation[3] of the Ar or RC═O substituents, when a nonplanar conformation is adopted.

Results and Discussion

Three types of conformers (Scheme 1) are expected to exist for compounds **1**−**3** when the substituents (Ar and RC═O) are not coplanar with the central phenyl group. Ab initio calculations[4] indicate that they do correspond to energy minima and also that the RC═O and the two external aryl groups are not

(1) In partial fulfillment for the Ph.D. in Chemical Sciences, University of Bologna.

(2) Lunazzi, L.; Mazzanti, A.; Minzoni, M.; Anderson, J. E. *Org. Lett.* **2005**, *7*, 1291.

(3) (a) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1. (b) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307. (c) Eliel, E. L. *J. Chem. Educ.* **1980**, *57*, 52.

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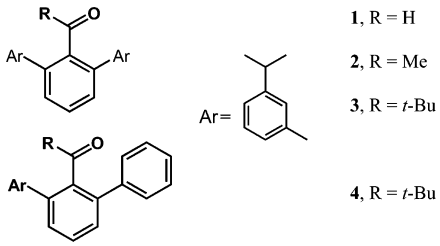
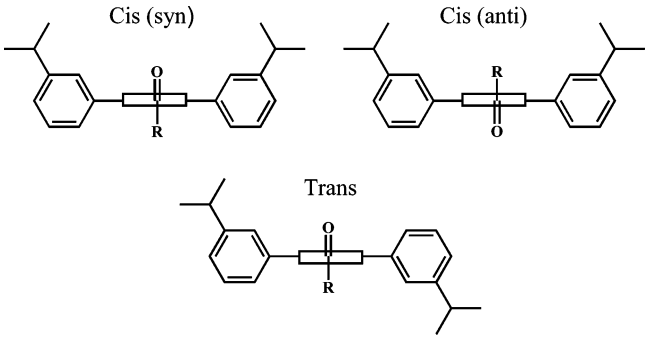
CHART 1



SCHEME 1[a]



[a] In the two cis atropisomers the position of the isopropyl groups closer to oxygen identifies the structure as syn, that of the isopropyl groups farther away from oxygen identifies the structure as anti.

coplanar with the central ring, although not always exactly orthogonal, as displayed in Scheme 1. However, the torsion process about the orthogonal position is predicted to have such a low barrier (in the case of **1**, for instance, this barrier is computed to be as low as 4.0 kcal mol^{-1} for the torsion of the HC═O group and 1.0 kcal mol^{-1} for the aryl−aryl torsion) that for most purposes these compounds can be considered as having the symmetry shown in Scheme 1 (i.e., C_s for the two cis atropisomers and C_1 for the trans atropisomer).

In Figure 1 is reported the ^{13}C NMR signal of the isopropyl methyl groups of **1** (R = H) as a function of temperature. At −141 °C four lines are observed: the spectral simulation indicates that their relative intensities are essentially the same. This means that two nearly equally populated conformers are present, each displaying a pair of diastereotopic methyl groups. Almost all the other ^{13}C lines of **1** are also split into nearly equally intense pairs at this temperature (see the Supporting Information, Figure S-1). Such an observation indicates that HC═O has a very fast rotation rate on the NMR time scale, so that the cis (syn) and cis (anti) conformers of Scheme 1 interchange too rapidly to be individually identified. Accordingly, only a single averaged cis conformer can be experimentally detected. The same fast process occurs in the trans C_1 conformer, which thus appears as having a "dynamic" C_2 symmetry. In other words, not only the torsion of the CH═O moiety through the orthogonal transition state is very rapid in **1**, but also the rotation process through the coplanar transition state is rapid (this barrier is computed[4] to be about 1 kcal mol^{-1}). Thus, the lines observed at −141 °C are the result solely of the restricted rotation about the bonds connecting the aryl rings. The Ar−C(O)H bond rotation is fast on the NMR time scale even at such low temperatures, indicating that the corresponding $\Delta G^{\ddagger}$ value should be less than 5 kcal mol^{-1} (this agrees well with the theoretical prediction of 4.0 kcal mol^{-1}, as in Table 1).

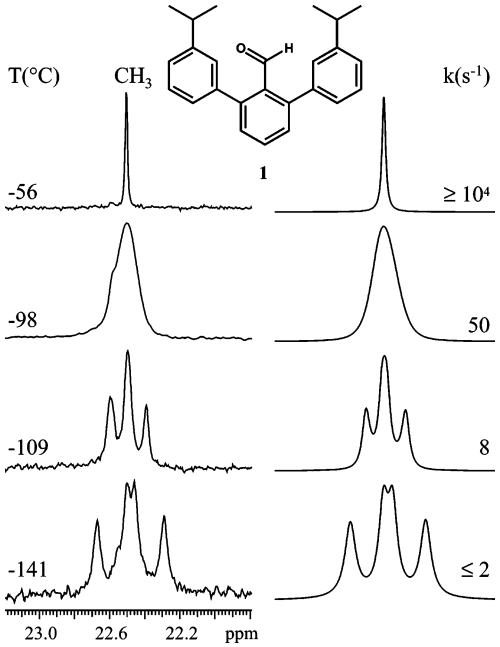


FIGURE 1. Left: temperature dependence of the ^{13}C (150.8 MHz) isopropyl methyl signal of **1** in $CHF_2Cl/CHFCl_2$. Right: simulation obtained with four equally intense lines and with the rate constants indicated.

TABLE 1. Experimental Barriers (kcal mol^{-1}) for the Bond Rotation Processes of 1−4[a]

compd	Ar−Ar rotation	Ar−C(O)R rotation	compd	Ar−Ar rotation	Ar−C(O)R rotation
1	8.7 (9.4)	<5 (4.0)	**3**	9.9 (10.1)	23.1 (22.3)
2	7.5_5 (7.8)	7.5_5 (8.0)	**4**	9.5 (10.1)	23.1 (22.3)

[a] In parentheses are given the ab initio computed values.

Line shape simulation of the spectrum of Figure 1 allowed us to obtain the rate constants for the interconversion between the trans and cis conformers of Scheme 1, the corresponding free energy of activation being 8.7 kcal mol^{-1} (Table 1). This result is further confirmed by the observation that the same $\Delta G^{\ddagger}$ value could also be obtained by line shape simulation of the two lines (149.4 and 149.8 ppm as in the Supporting Information, Figure S-1) due to the quaternary carbons bonded to the isopropyl substituent (identified by means of the gHMBC pulse sequence[5]). The ab initio computed barrier for such an Ar−Ar

(4) Gaussian 03, revision D.01: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; 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.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A., Gaussian Inc., Wallingford, CT, 2004.

(5) Hurd, R. E.; John, B. K. *J. Magn. Reson.* **1991**, *91*, 648.

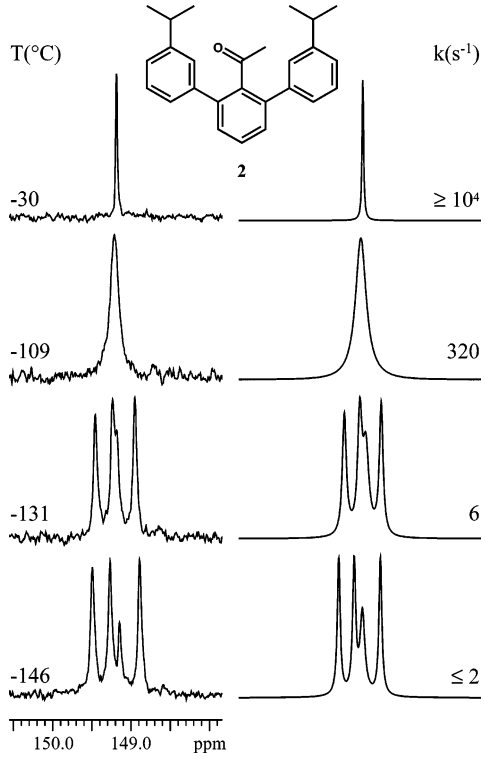


FIGURE 2. Left: temperature dependence of the ^{13}C (150.8 MHz) signal of the quaternary carbons bonded to the isopropyl groups of **2** in $CHF_2Cl/CHFCl_2$. Right: simulation obtained with the rate constants indicated.

rotation process (9.4 kcal mol^{-1}) is in good agreement with the experiment.[6]

The ^{13}C carbonyl signal of **2** (R = Me) at −146 °C shows three lines, with 32:58:10 relative integrated intensities (Supporting Information, Figure S-2). This means that all three possible conformers of Scheme 1 appear to be populated, a situation which requires that both the Ar−Ar and the Ar−C(O)-Me bond rotations are locked on the NMR time scale at this temperature. Information on the symmetry of the conformers can be obtained from the signals of the pairs of carbons. For instance, the spectrum due to the pair of quaternary carbons bonded to the isopropyl group (identified by the gHMBC pulse sequence[5]) displays four lines with relative integrated intensities of 32:29:10:29 (Figure 2). Thus, the two equally intense lines (29 ± 1% each) must be assigned to the asymmetric trans conformer (C_1 point group), whereas the other two (32 ± 1% and 10 ± 1%) belong to the cis conformers, because both have a plane of symmetry (C_s point group). It was impossible for us to identify which is the more stable of the two cis conformers solely on experimental grounds, so we made use of the ab initio computations to help in the assignment. The values of the relative energies calculated in this way are 0, 0.08, and 0.16 kcal mol^{-1} for the cis (syn), trans, and cis (anti) conformers, respectively. The cis (anti) structure is the least stable and should be thus assigned to the conformer displaying the 10% population in the experimental spectrum. These computations match the experimental trend of the populations since it has to be taken into account that the most populated trans form (58%) can be obtained by rotation of either of the two external aryl rings; thus, it is 2-fold degenerate with respect to its cis companions: in other words, this degeneracy is a consequence of the existence of two enantiomeric forms, due to the chirality of the trans conformer. The thermodynamic stability of the trans structure corresponds, accordingly, to a population of 1/2 × 58% = 29%, and if this statistical correction is taken into account, the trans structure appears to be the second most stable conformer, in qualitative agreement with its computed relative energy of 0.08 kcal mol^{-1}. On this basis, the cis (syn) structure, computed to be the most stable, must be assigned to the conformer with the 32% population.[7]

The line shape simulation (Figure 2) could be performed by using the same rate constant for both the Ar−Ar and the Ar−C(O)Me rotation processes. This means that the two barriers are indistinguishable within the experimental accuracy, their values being 7.5_5 ± 0.2 kcal mol^{-1}, as in Table 1. Such a near identity is confirmed by computations that predict barriers of 7.8 and 8.0 kcal mol^{-1} for the Ar−Ar and Ar−C(O)Me bond rotations, respectively. The fact that both these motions become rapid above −110 °C, as shown in Figure 2, is further confirmed by the observation that also the isopropyl methyl groups, which appear diastereotopic[3] at −146 °C, become equivalent (enantiotopic) on raising the temperature, eventually displaying a single ^{13}C line: in these conditions, in fact, the molecule has achieved a dynamic C_{2v} symmetry.

It might seem quite surprising that the Ar−Ar rotation barrier of **2** is somewhat lower (by 1.2 kcal mol^{-1}) than that of **1** (Table 1). This feature is most likely a consequence of the different dihedral angles adopted by the RC═O moieties with respect to the central aryl ring. In the case of **1** (R = H) this angle is computed to be only 28°, whereas in **2** (R = Me) it is 88°. Due to its orthogonal arrangement, the MeC═O moiety exerts a steric interaction smaller than that of the nearly coplanar HC═O group toward the external isopropylphenyl rings: for this reason the HC═O moiety behaves, in practice, as a bulkier group as far as the Ar−Ar rotation is concerned.

The low-temperature (−115 °C) ^{13}C spectrum of the methyl groups of the *tert*-butyl moiety of **3** (Figure 3) displays three signals with a 48:40:12 peak surface ratio that coalesce into a single line above −74 °C. As in the case of **2** all three possible conformers are NMR visible in that both the Ar−Ar and the *t*-BuC(O)−Ar bond rotations are locked at this temperature.

The pair of quaternary carbons bonded to the isopropyl groups display four lines at −125 °C, their peak surface ratio being 12:20:48:20 (Supporting Information Figure S-3). The pair of equally intense lines (20% each) must thus be assigned to the trans conformer, which, accordingly, is present in a 40% proportion. By analogy with the methyl derivative **2**, the cis

(6) Since the cis to trans interconversion can be accomplished by the rotation of either of the two external aryl rings, the rate for the rotation of a single aryl ring corresponds to half of the measured rate constants. The corresponding barrier thus becomes 0.2 kcal mol^{-1} higher, and it is this value that, in principle, should be compared to the theoretical barrier.

(7) The analysis of the population distribution might also be performed by taking into account the entropy of mixing the conformational enantiomers (see: Eliel, L. E.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 97 and 601. Collet, A. In *Problems and Wonders of Chiral Molecules*; Simonyi, M., Ed.; Akadémiai Kiadó: Budapest, 1990; p 93). The computed energy (0.08 kcal mol^{-1}) of the chiral trans conformer is thus lowered by $RT \ln 2$ (i.e., 0.175 kcal mol^{-1} at −146 °C), becoming, therefore, 0.08−0.175 = −0.095 kcal mol^{-1}. On the basis of this correction, the previously computed relative energies of the three conformers (i.e., 0, 0.16, and 0.08 kcal mol^{-1}) become 0.095, 0.255, and 0 kcal mol^{-1} for cis (syn), cis (anti), and trans, respectively. These values correspond to theoretical populations of 33%, 18%, and 49%, respectively, a trend which parallels the experimental ratio of 32%, 10%, and 58%.

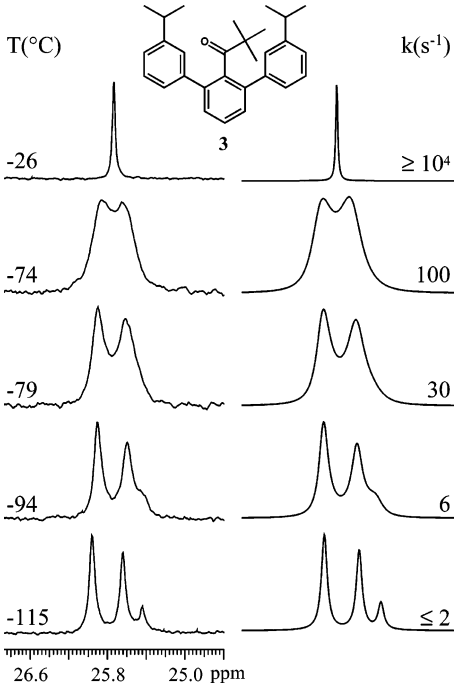


FIGURE 3. Left: temperature dependence of the *tert*-butyl methyl signal (^{13}C NMR at 150.8 MHz in $CHF_2Cl/CHFCl_2$) of **3**. Right: simulation obtained with the rate constants indicated.

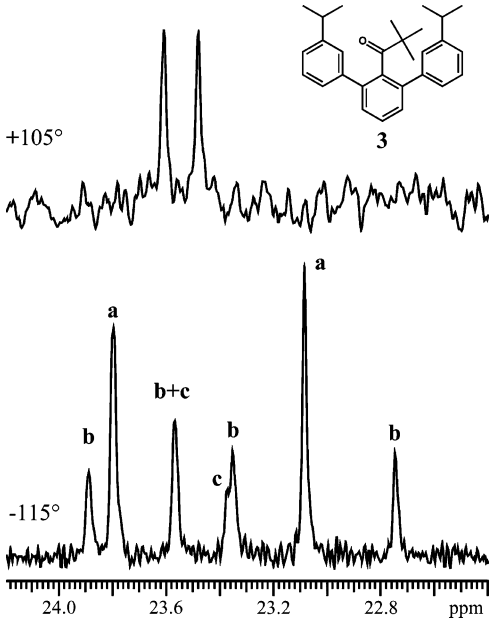


FIGURE 4. Bottom: ^{13}C NMR (150.8 MHz) signals of the isopropyl methyl groups of **3** at −115 °C in $CHF_2Cl/CHFCl_2$. The two lines labeled "a" belong to the cis (syn) conformer, the four lines labeled "b" to the trans conformer, and the two lines labeled "c" to the cis (anti) conformer. Top: same spectrum recorded at 105 °C in toluene-d_8.

(syn) structure should be assigned to the most populated (48%) conformer and the cis (anti) structure to the least populated (12%) conformer. This assignment is further supported by calculations that indicate how the trend for the relative computed energies is 0.0, 0.03, and 0.09 kcal mol^{-1} for the cis (syn), trans, and cis (anti) conformers, respectively.[8]

The spectrum of the isopropyl methyl groups of **3** at −115 °C (Figure 4, bottom) displays seven out of the expected eight lines, owing to the accidental coincidence of two peaks.[9] On raising the temperature, these lines coalesce into a doublet, but even at 105 °C (Figure 4, top) do not exchange any further to yield a single line, contrary to the case of **2**. The plane of the *t*-BuC═O moiety is twisted with respect to the central aryl ring, but the corresponding rotation process has a barrier so high[10] that the molecule cannot achieve the mentioned dynamic C_{2v} symmetry, even when warmed well above ambient temperature: for this reason the isopropyl methyl groups of **3** always appear diastereotopic.[3] Accordingly, the barrier determined by means of the rate constants of Figure 3 ($\Delta G = 9.9$ kcal mol^{-1}) is due solely to the Ar−Ar bond rotation:[6] the corresponding computed value of 10.1 kcal mol^{-1} is in very good agreement with this value (Table 1).

The absence of a noticeable broadening of the isopropyl methyl lines of **3** (as shown in the top trace of Figure 4) prevented the determination of the *t*-BuC(O)−Ar rotation barrier by the coalescence method.[10] As an alternative technique we made use of a monodimensional EXSY experiment, which was performed at 107 °C on the ^{1}H isopropyl methyl lines (see the Experimental Section). This approach allows one to achieve meaningful measurements of rate constants smaller than those obtainable by the other method, and in this way (Supporting Information Figure S-4) a rate constant of 0.4 s^{-1}, corresponding to a $\Delta G^{\ddagger}$ value of 23.1 kcal mol^{-1} (Table 1), was derived for the rotation about the *t*-BuC(O)−Ar bond:[11] again the computed value (22.3 kcal mol^{-1}) matches reasonably well the experimental measurement.

The highly restricted rotation about the *t*-BuC(O)−Ar bond of **3** suggests that, in the analogous derivative **4**, where only one of the two external aryl rings bears the isopropyl substituent (Scheme 2), two enantiomers with a stability sufficient for allowing a physical separation should occur: a $\Delta G^{\ddagger}$ value of 23.1 kcal mol^{-1} implies, in fact, a half-life of about $2^1/_2$ h at 21 °C (an analogous type of enantiomers, generated, as in the present case, by the restricted rotation about the sp^2-sp^2 bond, could be separated, for instance, in the case of hindered naphthylimines[12]).

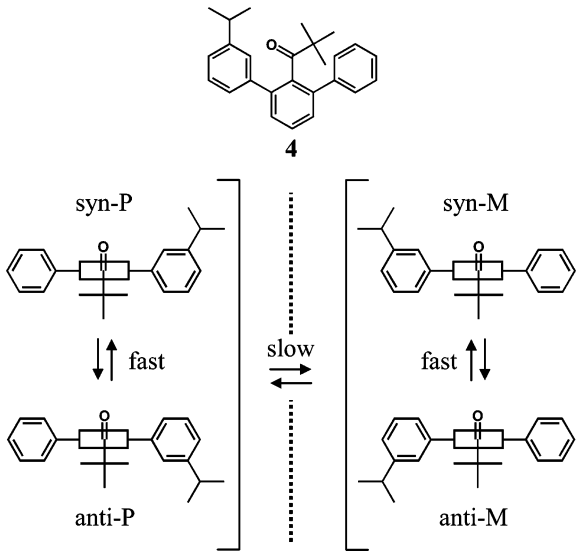
As shown in Scheme 2, two conformers (syn and anti) might be populated in **4**, each exhibiting a pair of M and P enantiomers. Owing to the fast syn to anti exchange[13] and to the mentioned slow M to P interconversion, the two "syn/anti

(8) Further support for this assignment was obtained by means of the computations of the ^{13}C chemical shifts (see the Experimental Section) of the trans conformer of **3**. These calculations indicate that the upfield shift of the quaternary carbon bonded to the isopropyl moiety corresponds to that in the ring having a syn relationship to C═O, the downfield shift being that in the anti relationship. The experimental signal of the same carbon of the major (48%) cis conformer is very close to the upfield shift of the trans conformer, whereas the experimental signal of the minor (12%) cis conformer is close to the downfield shift of the trans conformer (Supporting Information Figure S-3). On this basis, it is thus conceivable to assign the cis (syn) structure to the major conformer and the cis (anti) structure to the minor conformer, in agreement with the trend of the computed energies.

(9) The integrated intensity distribution of the isopropyl methyl lines matches the ratio 47:40:13 derived from the other signals. In particular, the four lines expected for the trans isomer correspond to the 40% intensity.

(10) Not even at 130 °C (in tetrachloroethane-d_2 as solvent) could we detect any appreciable broadening of the ^{1}H isopropyl methyl lines of **3**, thus suggesting that the *t*-BuC(O)−Ar rotation barrier must be larger than 22.5 kcal mol^{-1}. This lower limit derives from the consideration that a rate constant of at least 5 s^{-1} is usually needed to obtain a clearly noticeable broadening caused by an exchange process (see, for instance, Figures 2 and 3). Since in the present case the rate constant at 130 °C is certainly lower than 5 s^{-1}, the $\Delta G^{\ddagger}$ value should be consequently higher than 22.5 kcal mol^{-1}.

SCHEME 2



averaged" enantiomers were actually observed at ambient temperature by NMR in a chiral environment,[14] as displayed in Figure 5.

These enantiomers could even be separated by HPLC at 21 °C using an enantioselective column (Experimental Section): the oppositely phased CD spectra of these enantiomers (recorded at 10 °C to avoid racemization) are displayed in Figure 6.

The kinetics of the racemization process was followed by monitoring the decrease of the HPLC peak of the second eluted isolated enantiomer, accompanied by a simultaneous increase of the peak of its first eluted companion, until the two peaks again reached the same intensity: in this way a rate constant of 4×10^{-5} s^{-1} was obtained at 21 °C (Supporting Information Figure S-5). This rate corresponds to a free energy of activation of 23.1 kcal mol^{-1} (Table 1), a value equal, as conceivable,[15] to that obtained via NMR for the extremely similar derivative **3**.

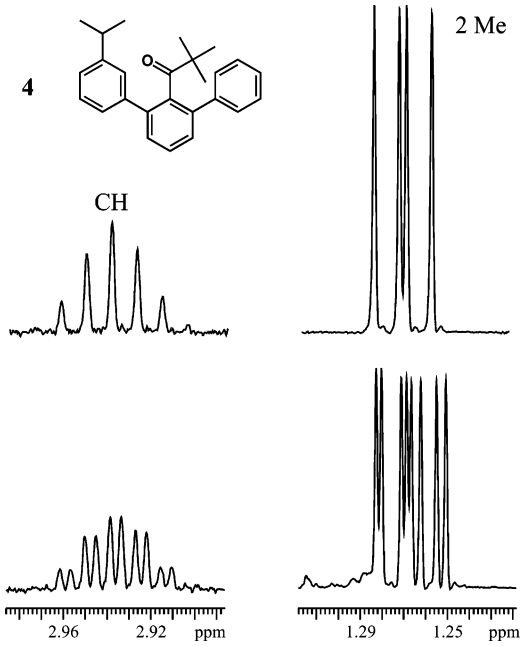


FIGURE 5. Top: ambient-temperature ^{1}H NMR signals (600 MHz in $CDCl_3$) of the CH and of the diastereotopic Me groups of the isopropyl moiety of **4**. Bottom: same spectrum in a chiral environment[14] exhibiting a splitting of all the lines, due to the M and P enantiomers.

Experimental Section

Materials. 2,6-Dibromobenzaldehyde[16] and 3-Isopropyl-phenylboronic acid[17] were prepared according to the literature. Phenylboronic acid was commercially available.

1-(2,6-Dibromophenyl)-2,2-dimethylpropan-1-one. A solution of lithium diisopropylamide was prepared in 1 h by addition of 6.3 mL of *n*-butyllithium (10 mmol, 1.6 M in hexane) to a stirred solution of 1.08 g of diisopropylamine (10 mmol in 40 mL of anhydrous THF) kept at −5 °C. The solution was then slowly transferred into a solution of 1,3-dibromobenzene (1.87 g, 8 mmol in 30 mL of anhydrous THF) kept at −78 °C. After 1 h the suspension of the resulting lithiate was treated with trimethylacetaldehyde (1.72 g, 20 mmol in 10 mL of THF). After 1 h at −78°, the mixture was warmed to ambient temperature and quenched with aqueous NH_4Cl. The extracted organic layer (Et_2O) was dried (Na_2SO_4) and evaporated, and the crude was treated with pyridinium chlorochromate (3.45 g, 16 mmol in 20 mL of CH_2Cl_2) at room temperature for about 1 h, following the reaction by GC−MS. The suspension was then filtered on silica and purified by chromatography on silica gel (hexane/Et_2O, 10:1) to obtain 2.27 g (7.1 mmol, 88%) of a white solid. Mp: 79−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 1.38 (9H, s) 7.08 (1H, t, J = 8.1 Hz), 7.53 (2H, d, J = 8.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ 28.7 (CH_3), 44.2 (q), 118.1 (q), 130.4 (CH), 131.9 (2CH), 144.0 (q), 211.5 (CO).

2,6-Bis(3-isopropylphenyl)benzaldehyde (1). To a solution of 2,6-dibromobenzaldhyde (0.264 g, 1 mmol in 6 mL of benzene) were added K_2CO_3 (2 M solution, 1.25 mL), 3-isopropylphenylboronic acid (0.410 g, 2.5 mmol, suspension in 6 mL of ethanol), and $Pd(PPh_3)_4$ (0.231 g, 0.2 mmol) at room temperature. The stirred

(11) This value can still be compared to those obtained at lower temperatures since the conformational processes have free energies of activation nearly independent of temperature, due to the negligible contribution of the $\Delta S^{\ddagger}$ values. See, for instance: Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484. Forlani, L.; Lunazzi L.; Medici, A. *Tetrahedron Lett.* **1977**, *18*, 4525. Bernardi, F.; Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron* **1977**, *33*, 1337. Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031. Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1990**, *112*, 2915. Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731. Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924. Garcia, M. B.; Grilli, S., Lunazzi, L.; Mazzanti, A., Orelli, L. R. *J. Org. Chem.* **2001**, *66*, 6679. Garcia, M. B.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Orelli, L. R. *Eur. J. Org. Chem.* **2002**, 4018. Casarini, D.; Rosini, C.; Grilli, S; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2003**, *68*, 1815. Casarini, D.; Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2004**, *69*, 345. Bartoli, G.; Lunazzi, L.; Massacesi, M.; Mazzanti, A. *J. Org. Chem.* **2004**, *69*, 821. Casarini, D.; Coluccini, C.; Lunazzi, L.; Mazzanti, A.; Rompietti, R. *J. Org. Chem.* **2004**, *69*, 5746.

(12) Casarini, D.; Lunazzi, L.; Macciantelli D. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1363

(13) Low-temperature NMR spectra of **4** show that the syn (65%) to anti (35%) interconversion has a barrier (9.5 ± 0.2 kcal mol^{-1}) equal, within the uncertainity, to that of the very similar compound **3** (Table 1). Again calculations predict that the conformer with the less crowded syn structure is more stable (by 0.1 kcal mol^{-1}) than the anti structure.

(14) Use was made of a 60:1 molar excess of the enantiopure (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem* **1977**, *42*, 384).

(15) The identity of the two $\Delta G^{\ddagger}$ values measured at temperatures as different as 21 and 107 °C (for the nearly equal compounds **4** and **3**, respectively) further supports the consideration that the term $\Delta S^{\ddagger}$ is negligible in the majority of conformational processes, as reported in ref 11.

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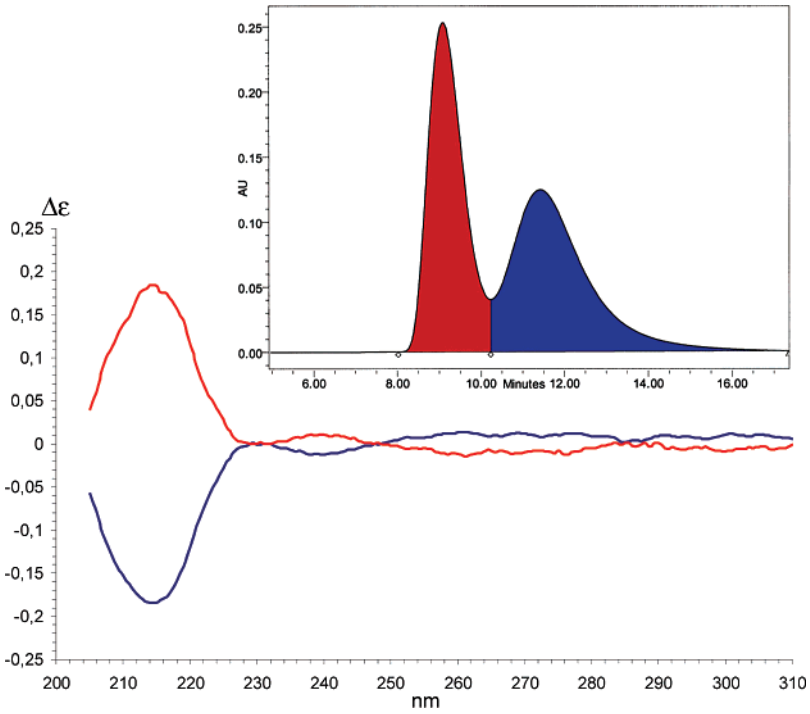

FIGURE 6. Top: HPLC resolution of the two enantiomers of **4** at 21 °C. Bottom: CD spectra (at 10 °C) of the first (red) and second (blue) eluted enantiomers.

solution was refluxed for 2−3 h, the reaction being monitored by GC−MS. Then $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude was purified by chromatography on silica gel (hexane/Et_2O, 20:1) to yield 0.270 g (0.79 mmol, 79%). Analytically pure samples were obtained by semipreparative HPLC (5 μm, 250 × 10 mm column, 5 mL/min, ACN/H_2O, 95:5, v/v). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 1.28 (12H, d, J = 6.8 Hz), 2.95 (2H, septet, J = 6.8 Hz), 7.17−7.58 (11H, m). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 24.0 (CH_3), 34.0 (CH), 125.7 (CH), 127.0 (CH), 127.9 (CH), 128.0 (CH), 130.2 (CH), 131.3 (CH), 133.4 (q), 139.6 (q), 144.5 (q), 148.7 (q), 193.8 (CO). HRMS (EI): m/z calcd for $C_{25}H_{26}O$ 342.19836, found 342.19761.

2,6-Bis(3-isopropylphenyl)acetophenone (2). To a solution of 2,6-bis(3-isopropylphenyl)benzaldehyde (0.342 g, 1 mmol in 10 mL of THF) kept at −78 °C was added a solution of MeLi (1.6 mL, 2.4 mmol in Et_2O). After 1 h at −78 °C, the stirred solution was warmed to ambient temperature and quenched with aqueous NH_4Cl, and the organic layer was extracted with Et_2O and dried (Na_2SO_4). The crude was then treated with pyridinium chlorochromate (0.77 g, 3.0 mmol in 10 mL of CH_2Cl_2) at room temperature for about 1 h, following the reaction by GC−MS. The suspension was then filtered on silica and purified by chromatography on silica gel (hexane/Et_2O, 10:1) to obtain 0.310 g (0.87 mmol, 87%) of the product. Analytically pure samples were obtained by semipreparative HPLC (5 μm, 250 × 10 mm column, 5 mL/min, ACN/H_2O, 95:5, v/v). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 1.26 (12H, d, J = 6.9 Hz), 1.86 (3H, s), 2.93 (2H, septet, J = 6.9 Hz), 7.18−7.47 (11H, m). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 23.9 (CH_3), 32.8 (CH_3), 34.0 (CH), 125.7 (CH), 126.4 (CH), 127.4 (CH), 128.3 (CH), 128.5 (CH), 129.0 (CH), 139.4 (q), 140.3 (q), 141.4 (q), 148.9 (q), 206.4 (CO). HRMS (EI): m/z calcd for $C_{26}H_{28}O$ 356.21402, found 356.21358.

1-[2′,6′-Bis(3-isopropylphenyl)phenyl]-2,2-dimethylpropan-1-one (3). To a solution of 2,6-bis(3-isopropylphenyl)benzaldehyde (0.342 g, 1 mmol in 10 mL of THF) kept at −78 °C was added a solution of t-BuLi (1.7 mL, 2.5 mmol in pentane). After 1 h at −78 °C, the stirred solution was warmed to ambient temperature and quenched with acqueous NH_4Cl, and the organic layer was extracted with Et_2O and dried (Na_2SO_4). The crude was then treated with pyridinium chlorochromate (0.77 g, 3.0 mmol in 10 mL of CH_2Cl_2) at room temperature for about 1 h, following the reaction by GC−MS. The suspension was then filtered on silica and purified by chromatography on silica gel (hexane/Et_2O, 10:1) to obtain 0.340 g (0.85 mmol, 85%) of the product. Analytically pure samples were obtained by semipreparative HPLC (5 μm, 250 × 10 mm column, 5 mL/min, ACN/H_2O, 95:5, v/v). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 0.30 (9H, s), 1.25 (6H, d, J = 6.9 Hz), 1.27 (6H, d, J = 6.9 Hz), 2.92 (2H, septet, J = 6.9 Hz), 7.16−7.22 (4H, m), 7.27−7.31 (4H, m), 7.33 (2H, d, J = 7.6 Hz), 7.45 (1H, dd, J = 8.1, 7.3 Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 23.9 (CH_3), 24.0 (CH_3), 27.0 (CH_3), 34.1 (CH), 44.2 (q), 125.6 (CH), 127.8 (CH), 127.99 (CH), 128.01 (CH) 128.6 (CH), 129.2 (CH), 138.2 (q), 140.5 (q), 141.0 (q), 148.6 (q), 216.4 (CO). HRMS (EI): m/z calcd for $C_{29}H_{34}O$ 398.26097, found 398.26031.

1-[2′-(3-isopropylphenyl)-6′-phenylphenyl]-2,2-dimethylpropan-1-one (4). To a solution of 1-(2,6-dibromophenyl)-2,2-dimethylpropan-1-one (0.320 g, 1 mmol, in 6 mL of benzene) were added K_2CO_3 (2 M solution, 1.25 mL), 3-isopropylphenylboronic acid (0.164 g, 1.0 mmol, suspension in 3 mL of ethanol), and Pd(PPh_3)$_4$ (0.231 g, 0.2 mmol) at room temperature. The stirred solution was refluxed for 2−3 h, the reaction being monitored by GC−MS. After the solution was cooled to room temperature, phenylboronic acid (0.244 g, 2.0 mmol, suspension in 6 mL of ethanol) and Pd(PPh_3)$_4$ (0.231 g, 0.2 mmol) were then added, and the solution was refluxed again for 2 h. Then $CHCl_3$ and H_2O were added, and the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude was prepurified by chromatography on silica gel (hexane/Et_2O, 20:1) to yield a fraction containing the title compound together with compound **3** and 1-[2′-bromo-6′-(3-isopropylphenyl)phenyl]-2,2-dimethylpropan-1-one. Analytically pure samples of **4** were obtained by semipreparative HPLC (5 μm, 250 × 10 mm column, 5 mL/min, ACN/H_2O, 95:5, v/v). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 0.31 (9H, s), 1.254 (6H, d, J = 6.9 Hz), 1.270 (6H, d, J = 6.9 Hz), 2.92 (2H, septet, J = 6.9 Hz), 7.16 7.22 (4H, m), 7.28−7.38 (7H, m), 7.40−7.42 (2H, m),

7.46 (1H, t, $J = 7.7$ Hz). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C, TMS): δ 23.8 (CH_3), 24.0 (CH_3), 27.1 (CH_3), 34.1 (CH), 44.2 (q), 125.7 (CH), 127.5 (CH), 127.8 (CH), 127.9 (CH), 128.02 (CH), 128.06 (CH), 128.7 (CH), 129.3 (CH), 130.7 (CH), 137.9 (q), 138.3 (q), 140.4 (q), 140.6 (q), 140.9 (q), 148.6 (q), 216.4 (CO). HRMS (EI): *m*/*z* calcd for $C_{26}H_{28}O$ 356.21402, found 356.21321.

NMR Spectroscopy. The spectra were recorded at 400 and 600 MHz for ^{1}H and 100.6 and 150.8 MHz for ^{13}C. The assignments of the ^{13}C signals were obtained by bidimensional experiments (edited gHSQC[18] and gHMBC[5] sequences). The samples for obtaining spectra at temperatures lower than −100 °C were prepared by connecting to a vacuum line the NMR tubes containing the compound and some C_6D_6 for locking purposes and condensing therein the gaseous CHF_2Cl and $CHFCl_2$ (4:1, v/v) under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a Cu/Ni thermocouple before the measurements. Low-temperature ^{13}C spectra were acquired with a 5 mm dual probe, without spinning, with a sweep width of 38000 Hz, a pulse width of 4.9 μs (70° tip angle), and a delay time of 2.0 s. Proton decoupling was achieved with the standard Waltz-16 sequence. A line broadening function of 1−5 Hz was applied to the FIDs before Fourier transformation. Usually 512−1024 scans were acquired. Both peak integration and spectra deconvolution were used to determine the intensity ratios. The line shape simulations were performed by means of a PC version of the QCPE program DNMR 6 no. 633, Indiana University, Bloomington, IN. The monodimensional EXSY experiments were obtained in toluene-d_8 at 107 °C by means of the DPFGSE-NOE[19] sequence, raising the mixing time from 20 to 500 ms. To selectively irradiate the upfield doublet of the isopropyl methyl group, a 10 Hz wide shaped pulse was calculated with a refocusing SNOB shape[20] and a pulse width of 185 ms.

Calculations. Computations were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[4] (see the Supporting Information): the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed. The reported energy values are not ZPE corrected. Harmonic vibrational frequencies were calculated for all the stationary points. For each optimized ground state the frequency analysis showed the absence of imaginary frequencies, whereas each transition state showed a single imaginary frequency. Visual inspection of the corresponding normal mode was used to confirm that the right transition state had been found. NMR chemical shift calculations were obtained with the GIAO method at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level. TMS, calculated at the same level of theory,[21] was used as a reference to scale the absolute shielding value.

Enantioselective HPLC. Separation of the two atropisomers of **4** was obtained at 21 °C on a 250 × 4.6 mm column, at a flow rate of 0.5 mL/min, using hexane/*i*-PrOH, 98:2, v/v, as the eluent. UV detection was fixed at 225 nm. To avoid racemization, the two fractions were collected directly into refrigerated (−20 °C) containers.

CD Spectra. UV/vis absorption spectra of compound **4** in hexane/*i*-PrOH, 98:2, were recorded at 25 °C on the racemic mixture in the 350−190 nm spectral region. The cell path length was 0.1 cm. A concentration of compound **4** of 2.6×10^{-3} mol L^{-1} was used. CD spectra were recorded at 10 °C with the same path lengths of 0.1 cm, in the range 310−205 nm (the absorbance of the HPLC solvents obscured the region under 205 nm). Reported $\Delta\epsilon$ values are expressed as L mol^{-1} cm^{-1}.

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Supporting Information Available: ^{13}C NMR (at −141 °C) of the quaternary carbon spectral region of **1**, ^{13}C NMR (at −146 °C) of the carbonyl carbon spectral region of **2**, ^{13}C NMR signal of the isopropyl-bonded quaternary carbons of **3**, monodimensional EXSY spectra and kinetic data for **4**, time dependence of the enantioselective HPLC traces of **4**, ^{1}H NMR, ^{13}C NMR, and EI mass spectra of compounds **1**−**4** and of the precursor of **4**, HPLC traces of compounds **1**−**4**, and computational data for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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