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# Synthesis and Structural Characterization of New Cu(I) Complexes with the Antithyroid Drug 6-*n*-Propyl-thiouracil. Study of the Cu(I)-Catalyzed Intermolecular Cycloaddition of Iodonium Ylides toward Benzo[*b*]furans with Pharmaceutical Implementations

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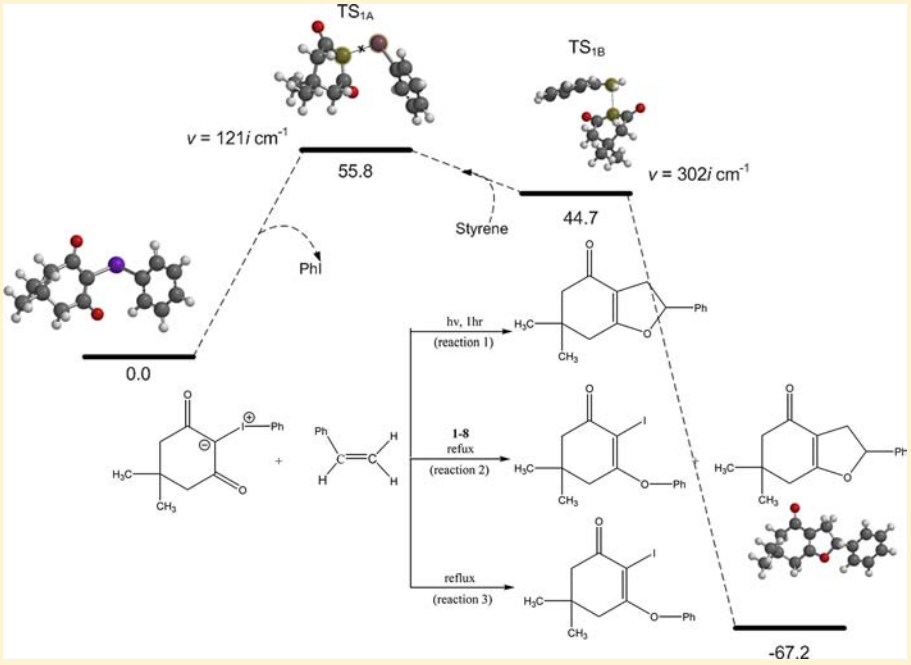
Supporting Information




**ABSTRACT:** The reaction of copper(I) iodide with 6-*n*-propylthiouracil (ptu) in the presence or absence of the triphenylphosphine (tpp) or tri(*p*-tolyl)phosphine (tptp) in a 1:1:2 molar ratio forms the mixed ligand Cu(I) complex with formula $[CuI(ptu)_2](toluene)$ (**1**), $[CuI(tpp)_2(ptu)]$ (**2**), and $[CuI(tptp)_2(ptu)]$ (**3**). The complexes have been characterized by FT-IR, $^1H$ NMR, UV−vis, spectroscopic techniques, and single crystal X-ray crystallography. Two sulfur atoms from two ptu ligands and one iodide form a trigonal geometry around the metal center in **1**. Intramolecular interactions through hydrogen bonds lead to a bend ribbon polymeric supramolecular architecture with zigzag conformation. Two phosphorus atoms from two arylphosphines, one sulfur atom, and one iodide anion form a tetrahedron around the copper ion in case of **2** and **3**. Intramolecular hydrogen bonding interactions lead to dimerization. Complexes **1**−**3** and the already known ones with formulas, $[(tpSb)_2Cu(\mu_2\text{-}I)_2Cu(tpSb)_2]$ (**4**) (tbSb = triphenylstibine), $[(tpp)Cu(\mu_2\text{-}I)_2Cu(tpp)_2]$ (**5**), $[(tpp)Cu(\mu_2\text{-}Cl)_2Cu(tpp)_2]$ (**6**), $[CuCl(tpp)_3\cdot(CH_3CN)]$ (**7**), and [AuCl(tpp)] (**8**), were used to study their catalytic activity on the intermolecular cycloaddition of iodonium ylides toward benzo[*b*]furans formation. The results show that both the metal and the ligand type affect the catalytic

*continued...*

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affinity of the complexes. The highest yield of benzo[*b*]furan was derived when complexes **2**, **3**, and **4** were used as catalysts. The mechanism of the Cu(I)-catalyzed and uncatalyzed intramolecular cycloaddition of iodonium ylide has been also thoroughly explored by means of ab initio electronic structure calculation methods, and the results are compared with the experimental ones.

## INTRODUCTION

Benzofurans and their derivatives have demonstrated a wide range of applications in modern pharmaceutical research.[1] Benzofurans are used as either pharmaceutical agents or basic precursors in the synthesis of important drugs such as antiallergic, antimicrobial, or anticancer drugs.[2−4] Recently, they have been studied as anti-HIV[3,4] agents and $\beta$-amyloid aggregation inhibitors.[1a,5] Therefore, the development of novel synthetic routes for benzofurans is of great interest. Toward this direction, the reaction of phenyliodonium dimedonate with unsaturated reagents for the formation of heterocyclic benzofurans (containing 5-member ring) (Scheme 1) was investigated since the late 80s.[6] The product (benzofurans) formation was found to depend upon irradiation, heating, and the presence of copper acetate (Scheme 1; reactions 1 and 2).[6] Products were obtained in relatively high yield.[6]

With no catalyst present an intramolecular rearrangement in phenyliodonium ylides might be also occurred leading to the formation of iodoether (Scheme 1; reaction 3). This was investigated theoretically in the case of intramolecular rearrangement in phenyliodonium ylides of hydroxyquinones.[7] It has been proposed that phenyliodonium ylides of hydroxyquinones easily undergo intramolecular rearrangements associated with phenyl-group migration or ketene formation.[7] Phenyl- group migration is favorable thermodynamically by heating the reaction mixture. The influence of the catalyst upon the product formation is still a matter of investigation since the development of new catalyst for the synthesis of new benzofuran derivatives is of great importance. Thus, several catalysts and catalytic systems such as $[Rh(CO)_2acac]$,[8a] $[Rh_2(OAc)_4]$,[8b] $[Pd(OAc)_2]/[CuI]$,[8c] $[Pd(PPh_3)_4]$,[8d] $[Cu(OTf)_2]$,[8e] $[Cu(phen)(PPh_3)]NO_3$,[8e] $[Ph_3PAuNTf_2]$,[8f] $[MePosAuCl]/AgNTf_2$,[8f] etc. have been used with various degrees of success in yield and time and cost effectiveness. Copper based catalysts efficiently indulge these requirements.[8e]

Copper(I) ion, on the other hand, is an important metal ion which has a strong tendency to form covalent bonds with ligands containing S or P donor atoms.[9] Copper compounds often show short Cu−Cu contacts (known as cuprophilicity)[9] which are less than twice the van der Waals radius of Cu (2.00−2.27 Å).[10] This results in the formation of oligomers and polymers with various coordination network types, leading to a new type of aromaticity, due to a cyclical delocalization of d as well as (d−p) $\pi$-type orbital electron density instead of the usual p orbitals on metal−ligand rings,[11] which may introduce greater stability to the higher-order structures. The ligand 6-*n*-propyl-2-thiouracil (ptu) is among the most commonly employed antithyroidal drugs in use, for the treatment of hyper-thyroidism (Graves′ disease).[12a] It is found to inhibit the formation of 3,5,3′-triiodothyronine (**T3**) and 3,5,3′,5′-tetraiodothyronine (**T4**) hormones, by blocking the metabolism of iodine.[12b] The use of the thioamide ptu as ligand in the synthesis of the Cu(I) catalysts **1**−**3** was chosen because (i) ptu covers the chemical demands of the soft acid, copper(I) ion, for soft ligands (sulfur donor atoms), (ii) it stabilizes the copper(I) oxidation state, and (iii) it allows the use of the product as catalyst for pharmaceutical processes since ptu is already a drug in use.

Here, we report the synthesis of new copper(I) complexes with formulas: $[CuI(ptu)_2](toluene)]$ (**1**), $[CuI(tpp)_2(ptu)]$ (**2**), and $[CuI(tptp)_2(ptu)]$ (**3**) (ptu = 6-*n*-propylthiouracil, tpp = triphenylphosphine, and tptp = tri(p-tolyl)phosphine (Scheme 2)). The complexes have been characterized by FT-IR, $^1$H NMR, UV−vis, spectroscopic techniques, and single crystal X-ray crystallography. Complexes **1**−**3** and the already known, $[(tpSb)_2Cu(\mu_2\text{-}I)_2Cu(tpSb)_2]$ (**4**) (tbSb = triphenylstibine), $[(tpp)Cu(\mu_2\text{-}I)_2Cu(tpp)_2]$ (**5**), $[(tpp)Cu(\mu_2\text{-}Cl)_2Cu(tpp)_2]$ (**6**), $[CuCl(tpp)_3\cdot(CH_3CN)]$ (**7**), and $[AuCl(tpp)]$ (**8**),[13,14] were used to study their catalytic activity on the intermolecular cycloaddition of iodonium ylides toward benzo[*b*]furans formation. The catalytic activity on the intermolecular cycloaddition of iodonium ylides toward benzo[*b*]furans formation caused by copper(II) ions $[Cu(acac)_2]^{2+}$ is already reported.[6] In order to ascertain whether this catalytic activity is a redox process or not, copper(I) iodide complexes **1**−**3** were designed and developed. Thus, copper(I) iodide compounds of ptu with and without tpp or tptp were used to ensure the Cu(I) oxidation state of the complex. Copper(I) complexes of thioamides with and without phosphines are known to exhibit structural diversity and often form oligomers and polymers with various coordination network types[9] allowing the structure−activity relationship (SAR) study of these compounds. Thereby, new, more efficient catalysts can be developed for this process.

## RESULTS AND DISCUSSION

**General Aspects.** Complexes **1**−**3** have been prepared by reacting copper(I) iodide with 6-*n*-propylthiouracil (ptu) in the presence or absence of the triphenylphosphine (tpp) or tri(p-tolyl)phosphine (tptp) in 1:1:2 molar ratio in methanole/acetonitrile 1:1 solution (Scheme 3). Crystals of complexes **2**−**3** have been prepared by slow evaporation of the solutions which remain after the filtration of the reaction solutions. In the case of **1**, crystals of the name compound were grown after recrystallization from toluene.

The crystals of complexes are air stable when they were kept in darkness at room temperature. The formulas of the complexes were first deduced from their m.p., their spectroscopic data, and single-crystal X-ray crystallography at ambient conditions. Compounds **4**−**8** were prepared by reacting copper(I) halide with tpp, tptp, or trriphenylstibine (tpSb) in proper molar ratios (1:2 (**4**), 2:3 (**5**,**6**), 1:3 (**7**), and 1:1 (**8**)) in methanole/acetonitrile 1:1 solution. Crystals of complexes **4**−**8** were analyzed by X-ray diffraction crystallography, and they were found to be identical with those already known.[13,14] Small differences in the unit cell parameters were only observed in case **4** where $a$ = 24.4463(6), $b$ = 13.9088(3), $c$ = 20.2168(5), and $\beta$ = 111.241(3)° in contrast to those already reported in ref 13a ($a$ = 24.620(9), $b$ = 14.090(4), $c$ = 20.382(9), and $\beta$ = 110.65(3)°). Scheme 4 shows the molecular formulas of complexes **4**−**8**.

**Crystal and Molecular Structures of $[CuI(ptu)_2]$·(toluene) (1), $[CuI(tpp)_2(ptu)]$ (2), and $[CuI(tptp)_2(ptu)]$ (3) Complexes.** The structures of complexes **1**−**3** were determined by X-ray diffraction at 100(2) K. Molecular diagrams of complexes **1**−**3** are shown in Figures 1−3, while selected bond distances and angles are given in Table 1.

Complexes **1**−**3** are monomers. Two sulfur atoms from two ptu ligands and one iodide ion are coordinated to Cu(I) cation forming a planar trigonal arrangement in case of **1** (Figure 1A).


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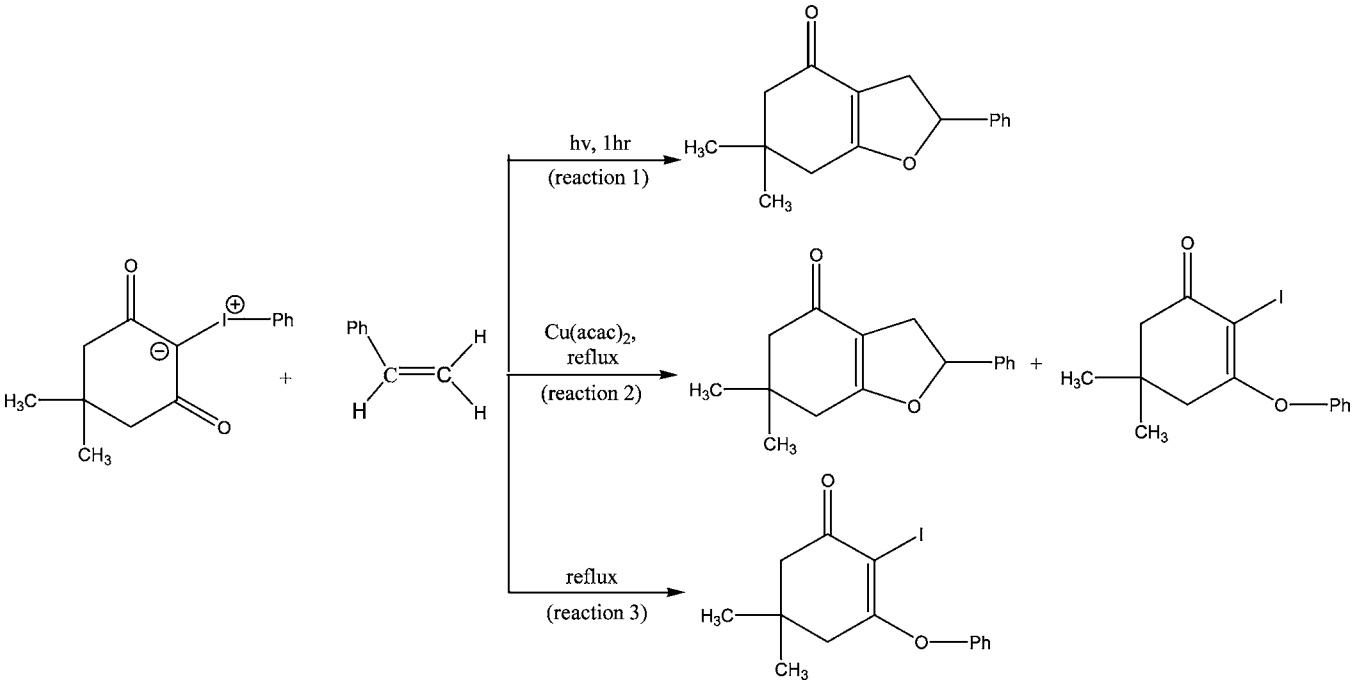
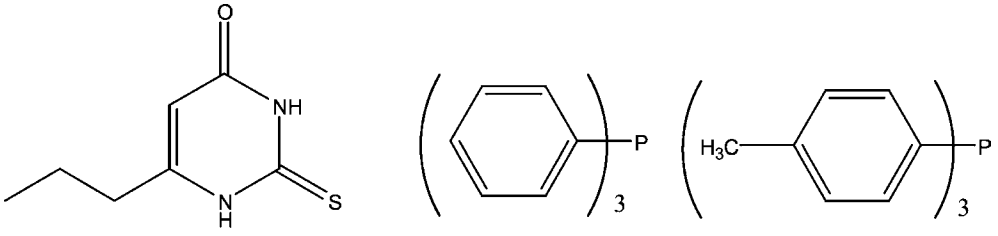
**Scheme 1**

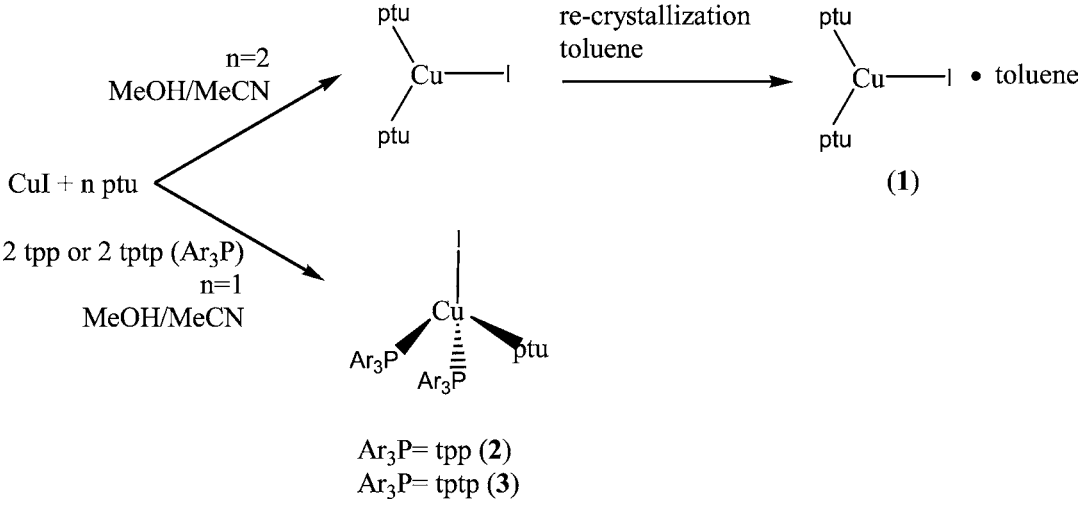



**Scheme 2**




**ptu** **tpp** **tptp**

**Scheme 3**




$Ar_3P$= tpp (**2**)
$Ar_3P$= tptp (**3**)

Two phosphorus from two tpp (**2**) or tptp (**3**) ligands, one iodide anion, and one sulfur atom from a ptu ligand are coordinated to the metal center in case of **2**, **3** leading to a tetrahedral arrangement around the copper(I) ion (Figures 2 and 3).

Structures of copper(I) iodide complexes with thioamides having trigonal geometry are rare. These include [Cu(totp)(tzdtH)I] (tzdtH = 1,3-thiazolidine-2-thione. totp = triortho-tolylphosphine),[15a] [Cu(dmimtH)$_2$I] (dmimtH = 1,3-dimethylimidazole-2-thione),[15b] [Cu(ettu)$_2$I] (ettu = *N*,*N*′-ethylenethiourea-S),[15c]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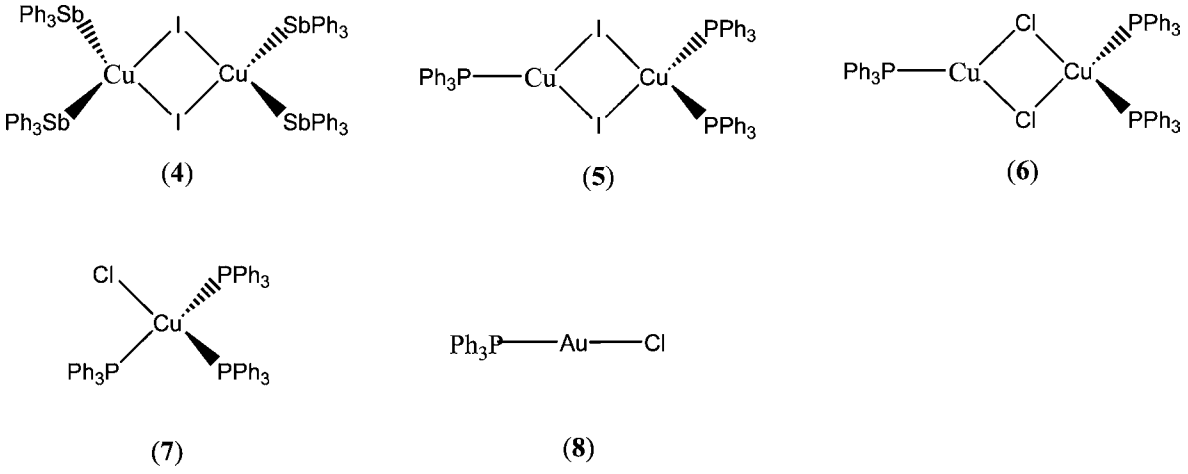
**Scheme 4**



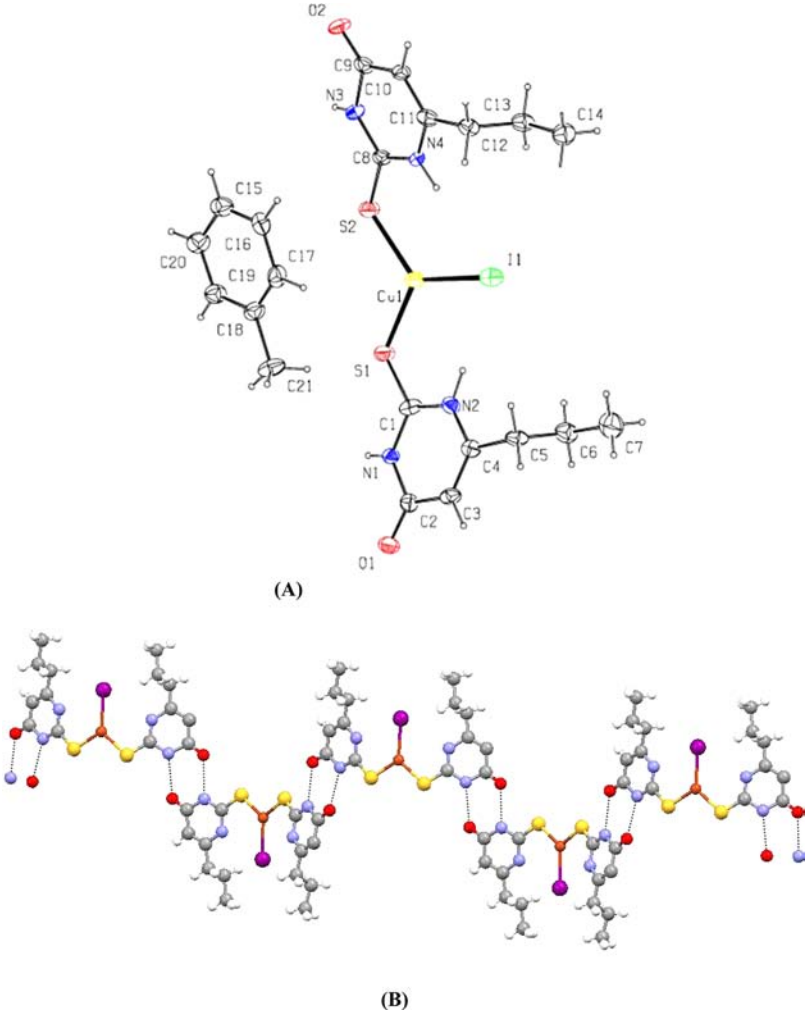




**Figure 1.** (**A**) Molecular diagram of compound **1** together with the atomic numbering scheme. (**B**) Intramolecular hydrogen bonting interactions lead to a bending 1D ribbon polymeric supra-molecular architecture with zigzag conformation.

$[Cu(tohmim)_2I]$ (tohmim = 2-thioxohexamethyleneimine),[15d] $[Cu(L)_2I]$ (L = 3-propylimidazolidine-2-thione),[15e] and $[Cu(L)_2I]$ (L = 3*N*-propylimidazolidine-2-thione).[15f] Examples of tetrahedral copper(I) iodide complexes with phosphines and thioamides on the other hand, include $[CuI(PPh_3)_2(bzimtH_2)]$ ($bzimtH_2$ = benz-1,3-imidazole-2-thione, $PPh_3$ = triphenyphosphine),[9b] $[CuI(PPh_3)_2(bztztH)]$ (bztztH = benz-1,3-thiazole-2-thione) (2.3660(6) Å),[9b] $[Cu(PPh_3)_2(pymtH)I]$ (pymtH = pyrimidine-2-thione),[16a] $[CuI(PPh_3)_2(mmi)]$ (mmi = 1-methylimidazole-2-thione),[16b] and $[CuI(PPh_3)_2(imtH)]$ (imtH = imidazoline-2-thione).[16c]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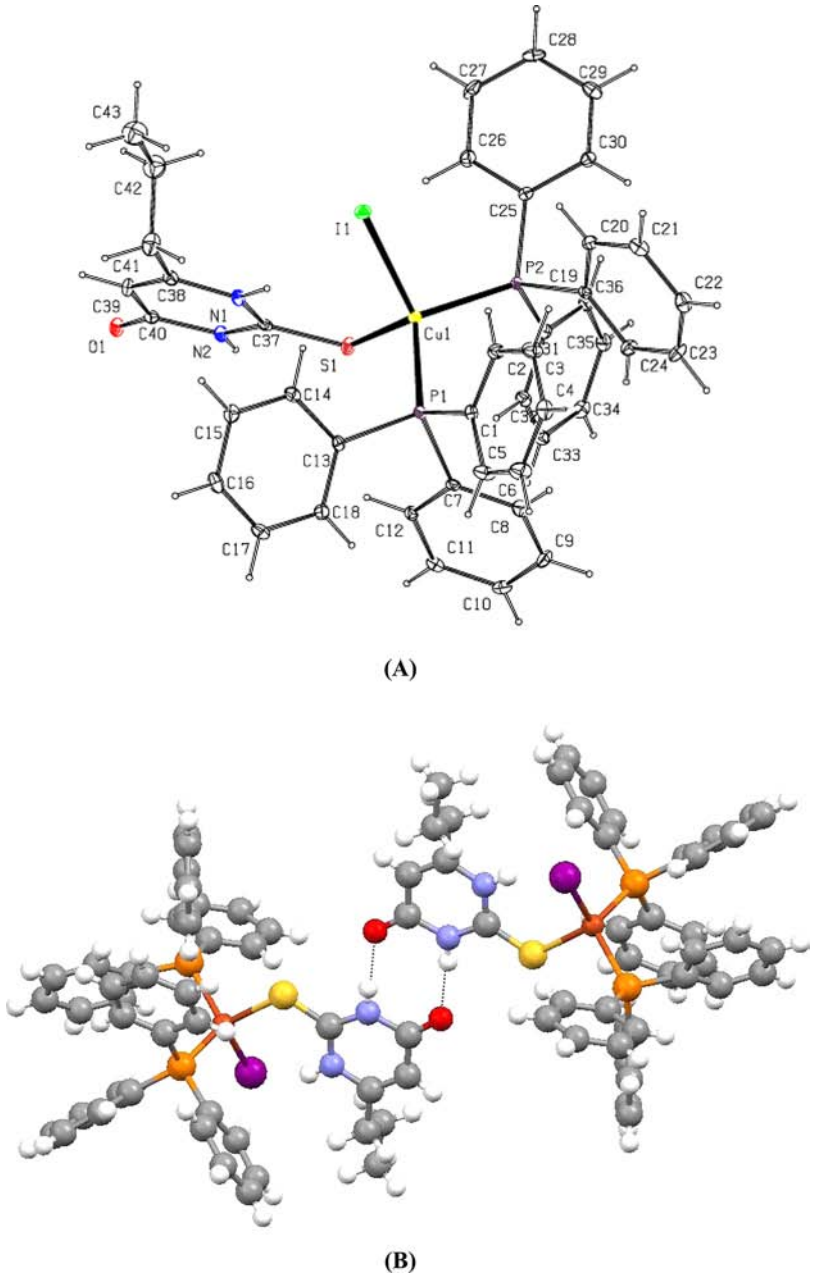


**Figure 2.** (**A**) Molecular diagram of compound **2** together with the atomic numbering scheme. (**B**) Intramolecular hydrogen bonding interactions lead to a dimerization.

The two Cu−S bond distances, in complex **1**, are 2.237(2) and 2.238(2) Å, respectively, which are in accordance to the corresponding ones found in copper(I)-thioamide complexes with trigonal geometry an in [Cu(totp)(tzdtH)I] (2.254(2) Å),[15a] in [Cu(dmimtH)$_2$I] (2.234 Å),[15b] [Cu(ettu)$_2$I] (2.239 Å),[15c] [Cu(tohmim)$_2$I] (2.238 and 2.248 Å),[15d] and [Cu(L)$_2$I] (2.227 and 2.240 Å).[15e] However, these Cu−S bond lengths are shorter than the corresponding ones found in mixed ligand copper(I) iodide complexes with tetrahedral geometry around the metal center as in [CuI(PPh$_3$)$_2$(bzimtH$_2$)] (2.3692(9) Å),[9b] in [CuI-(PPh$_3$)$_2$(bztztH)] (2.3660(6) Å),[9b] in [Cu(PPh$_3$)$_2$(pymtH)I] (2.338(4) Å),[16a] in [CuI(PPh$_3$)$_2$(mmi)] (2.369 Å),[16b] and [CuI(PPh$_3$)$_2$(imtH)] (2.344 Å).[16c]

The Cu−I bond distance in **1** is 2.5681(11) Å which is close with the Cu−I bond distance found in [Cu(totp)(tzdtH)I] complex (2.563(l) Å) of trigonal geometry around copper(I) ion[15a] in [Cu(dmimtH)$_2$I] (2.574 Å) [15b], [Cu(ettu)$_2$I] (2.555 Å),[15c] [Cu(tohmim)$_2$I] (2.590 Å),[15d] and [Cu(L)$_2$I] (2.531 Å),[15e] but shorter than those found in the complexes with tetrahedral geometry: [CuI(PPh$_3$)$_2$(bzimtH$_2$)] (2.6901(6),[9b] [CuI-(PPh$_3$)$_2$(bztztH)] (2.6807(3) Å),[9b] [Cu(PPh$_3$)$_2$(pymtH)I] (2.674(2) Å),[16a] in [CuI(PPh$_3$)$_2$(mmi)] (2.681 Å),[16b] and [CuI-(PPh$_3$)$_2$(imtH)] (2.673 Å).[16c]

The bond angles around the metal center (I1−Cu1−S1 = 124.19(6), I1−Cu1−S2 = 124.83(6), S1−Cu1−S2 = 110.98(8)°) (Figure 1A) varied from the ideal value of 120° due to different valence shell electron pair repulsions (VSEPR). This also explains why the I1−Cu1−S bond angles are higher compared to the S1−Cu1−S2 since the sulfur electronegativity is higher to the one of iodine.

Strong intramolecular hydrogen bonding interactions N1[H22]••O2 (2.748(8) Å) and N3[H24]••O1 (2.828(8) Å)


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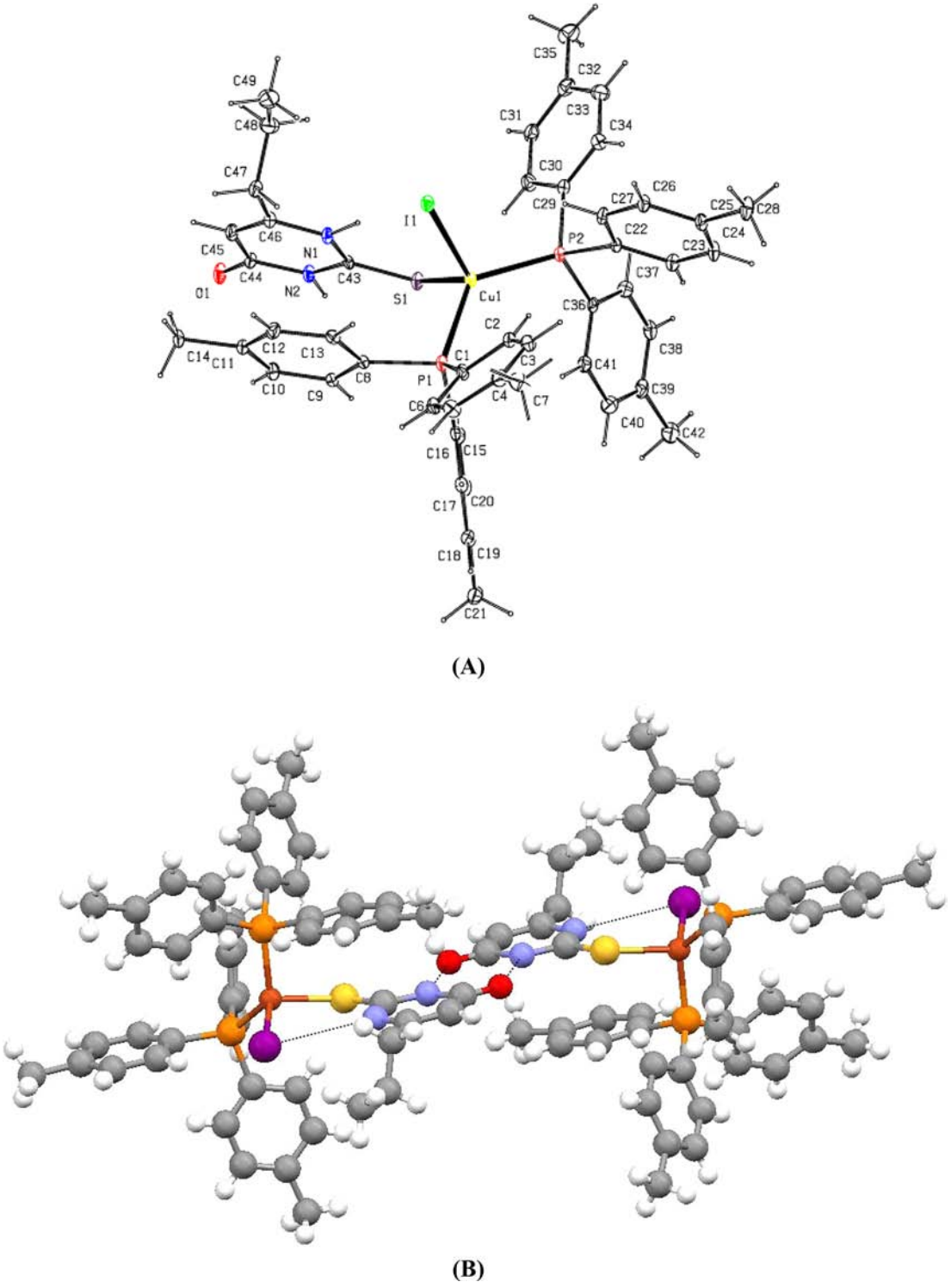


(A)

(B)

**Figure 3.** (**A**) Molecular diagram of compound **3** together with the atomic numbering scheme. (**B**) Intra- and intermolecular hydrogen bonds form a dimer with almost planar core.

lead to a bending 1D ribbon polymeric supramolecular architecture with zigzag conformation (Figure 1B).

The Cu−S bond distances in complexes **2**−**3** (2.3754(8) Å (**2**), 2.368(2) Å (**3**)) are in the range of the distances found in other copper(I) iodide complexes: 2.3692(9) Å, in [CuI-$(PPh_3)_2$(bztztH)] (bztztH = benz-1,3-thiazole-2-thione) (2.3660(6) Å),[9b] and in [$Cu(PPh_3)_2$(pymtH)I] (pymtH = pyrimidine-2-thione) (2.338(4) Å).[15b] The Cu−I bond lengths (2.6468(4) Å (**2**), 2.6660(12) Å (**3**)) are in accordance with the corresponding ones found in [$CuI(PPh_3)_2(bzimtH_2)$] (2.6901(6),[9b] [$CuI(PPh_3)_2$(bztztH)] (2.6807(3) Å),[9b] and [$Cu(PPh_3)_2$(pymtH)I] (2.674(2) Å).[15b] The Cu−P bonds, 2.2917(8) and 2.2840(7) Å (**2**) and 2.292(2) and 2.263(2) Å (**3**), are close to those found in [$CuI(PPh_3)_2(bzimtH_2)$] (2.2839(10) and 2.2796(9) Å),[9b] [$CuI(PPh_3)_2$(bztztH)] (2.2822(6) and 2.2796(6) Å),[9b] [$Cu(PPh_3)_2$(pymtH)I] (pymtH = pyrimidine-2-thione)


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**Table 1. Selected Bond Lengths (Å) and Angles (deg) of Complexes 1−3**

| complex 1 | | complex 2 | | complex 3 | |
|---|---|---|---|---|---|
| (a) bond lengths | | (a) bond lengths | | (a) bond lengths | |
| I1−Cu1 | 2.5681(11) | I1−Cu1 | 2.6468(4) | I1−Cu1 | 2.6660(12) |
| Cu1−S1 | 2.237(2) | Cu1−S1 | 2.3754(8) | Cu1−S1 | 2.368(2) |
| Cu1−S2 | 2.238(2) | Cu1−P1 | 2.2917(8) | Cu1−P1 | 2.292(2) |
| S1−C1 | 1.680(7) | Cu1−P2 | 2.2840(7) | Cu1−P2 | 2.263(2) |
| S2−C8 | 1.690(7) | S1 -C37 | 1.680(3) | S1−C43 | 1.672(9) |
| O1−C2 | 1.236(8) | | | | |
| O2−C9 | 1.199(9) | | | | |
| (b) angles | | (b) angles | | (b) angles | |
| I1−Cu1−S1 | 124.19(6) | I1−Cu1−S1 | 111.95(2) | I1−Cu1−S1 | 111.79(7) |
| I1−Cu1−S2 | 124.83(6) | I1−Cu1−P1 | 111.30(2) | I1−Cu1−P1 | 99.64(7) |
| S1−Cu1−S2 | 110.98(8) | I1−Cu1−P2 | 107.97(2) | I1−Cu1−P2 | 111.78(7) |
| | | S1−Cu1−P1 | 107.00(3) | S1−Cu1−P1 | 102.04(9) |
| | | S1−Cu1−P2 | 103.17(3) | S1−Cu1−P2 | 103.01(8) |
| | | P1−Cu1−P2 | 115.24(3) | P1−Cu1−P2 | 128.11(9) |
| hydrogen bonding interactions | | | | | |
| N1[H22]••O2 | 2.748(8) | N2[H44]••O1 | 2.794(3) | N2[H51]••O1 | 2.818(9) |
| N3[H24]••O1 | 2.828(8) | | | | |

(2.296(4) and 2.303(4) Å),[15a] and [Cu(totp)(tzdtH)I] (with trigonal geometry) where the Cu−P bond distance is 2.269(2) Å.[15a]

Strong intramolecular hydrogen bonding interactions (N2[H2]••O1 = 2.794(3) Å (**2**) and N2[H51]••O1 = 2.818(9) Å (**3**)) lead to dimerization (Figures 2B and 3B).

**Catalysis.** Complexes **1**−**8** were tested for their catalytic activity upon the reaction of phenyliodonium dimedonate, with phenyl-ethylene (styrene), for the formation of heterocyclic benzo[*b*]furans. Styrene was also the solvent media. The reaction mixture was refluxed at 114−118 °C under aerobic conditions for 3.5−4 min. The benzo[*b*]furan yielded was detected by the mean of HPLC (Table 2). The progress of the reaction is also monitored by $^1$H NMR spectroscopy. Figure 4 shows the $^1$H NMR spectra of ylide, styrene, iodoether, benzo[*b*]furan, and the reaction mixture of ylide with styrene catalyzed by complex **6**. The resonance signals at 1.06 and 1.05 ppm observed in the spectra of ylide and iodoether, respectively, are attributed to the proton of the methyl groups which are shifted at 1.16 ppm in the spectrum of benzo[*b*]furnan. The presence of both signals at 1.16 and 1.06 ppm in the reaction mixture is an indication of benzo[*b*]furnan product and iodoether as well.

The results show that copper(I) complexes (**1**−**7**) exhibit higher catalytic activity than the corresponding one of gold(I) (**8**). Among copper(I) complexes, the dimer **4** and the monomers **2**−**3** lead to the formation of benzo[*b*]furan in higher than 30% yield (**2** 26−33%; **3** 22−33%; and **4** 30−41%). Furthermore, both monomeric or dimeric copper(I) complexes with tetrahedral geometry around the metal center exhibit strong catalytic activity. Complexes **1**−**5** which contains iodo anion show better activity than the corresponding ones with chloride (**6**−**8**). Moreover, the kind of the ligand, affects on the catalytic activity of the complexes. Therefore, the synergistic effect of triphenystibine and iodide or thiarylphosphine and ptu ligands increases the catalytic ability of the complexes.

Although the high toxicity of antimony(III) compounds prohibits their usage as catalysts for pharmaceutical processes, complex **4** is studied for its catalytic activity in order to draw conclusion about the effect of the chemical composition of the ligands. Since complex **4** showed the higher catalytic activity it was used for detailed studies. Table 3 summarized the results. Although the amount of banzo[*b*]furan yielded remains unchanged when the amounts of catalyst and ylide are constant and the amount of styrene is decreased, the amount of iodoether derived is significantly lower. By increasing the amount of catalyst the amount of benzo[*b*]furan also increases as expected.

**Computational Studies.** The diverse behavior of phenyliodonium dimedonate in respect to its thermal transformation yielding either benzofuran (reaction 1) or iodoether (reaction 3) has motivated us to use theoretical calculations to understand the thermodynamics involved in these mechanisms. The potential energy reaction profiles for reaction 1, at the HF/3-21G* level, are depicted in Figure 5. The first reaction step involves the dissociation of iodobenzene (PhI) molecule from the (4,4-dimethyl-2,6-dioxocyclohexyl)(phenyl)iodonium via the

**Table 2. Catalytic Activity of 1−8 upon the Reaction of Phenyliodonium Dimedonate, with Styrene, for the Formation of Heterocyclic Benzo[*b*]furans and Iodoether**

| catalyst | MW | amount of catalyst (g) | reaction time (min) | ylide (g) | styrene (g) | catalyst/ylide/styrene molar ratio | benzo[*b*]furan (B)[a] (area, %) | iodoether (I)[b] (area, %) | ratio (B/I) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 622.91 | 0.00069 | 3.5 | 0.3099 | 0.5064 | 0.00111/0.90614/4.86923 | 27.3 | 20.2 | 1.35 |
| **2** | 884.68 | 0.00232 | 3.5 | 0.3042 | 0.5039 | 0.00262/0.88947/4.84519 | 25.7 | 24.9 | 1.03 |
| **2** | 884.68 | 0.00200 | 3.5 | 0.2965 | 0.5261 | 0.00226/0.86696/5.05865 | 32.7 | 12.8 | 2.55 |
| **2** | 884.68 | 0.00088 | 3.5 | 0.3029 | 0.5000 | 0.00099/0.88567/4.80769 | 27 | 10.3 | 2.62 |
| **3** | 968.68 | 0.00381 | 3.5 | 0.3451 | 0.5144 | 0.00393/1.00906/4.94615 | 22.0 | 26.0 | 0.85 |
| **3** | 968.68 | 0.00197 | 3.5 | 0.3146 | 0.5160 | 0.00203/0.91988/4.96154 | 25.2 | 19.3 | 1.31 |
| **3** | 968.68 | 0.00119 | 3.5 | 0.3118 | 0.5188 | 0.00123/0.91170/4.98846 | 33 | 21 | 1.57 |
| **4** | 1793.18 | 0.00371 | 3.5 | 0.3324 | 0.5198 | 0.00207/0.97193/4.99808 | 41.3 | 21.8 | 1.89 |
| **4** | 1793.18 | 0.00108 | 3.5 | 0.3326 | 0.5381 | 0.00060/0.97251/5.17404 | 36.5 | 11.1 (9) | 3.3 (4) |
| **4** | 1793.18 | 0.00452 | 3.5 | 0.3329 | 0.5090 | 0.00252/0.97339/4.89423 | 30.4 | 5.4 (5.0) | 5.6 (6) |
| **5** | 1166.9 | 0.00154 | 3.5 | 0.2980 | 0.4972 | 0.00132/0.87135/4.78077 | 13.3 | 45.7 | 0.3 |
| **5** | 1166.9 | 0.00424 | 3.5 | 0.2921 | 0.4986 | 0.00363/0.85409/4.79423 | 26.6 | 31.5 | 0.8 |
| **6** | 984 | 0.00484 | 3.5 | 0.3120 | 0.5346 | 0.00492/0.91228/5.14038 | 21.7 | 30.2 | 0.7 |
| **6** | 984 | 0.00341 | 3.5 | 0.3311 | 0.5534 | 0.00347/0.96813/5.32115 | 25.6 | 32.0 | 0.8 |
| **7** | 885 | 0.00395 | 3.5 | 0.2663 | 0.5442 | 0.00446/0.77865/5.23269 | 18.8 | 37.1 | 0.5 |
| **7** | 885 | 0.00253 | 3.5 | 0.3536 | 0.5135 | 0.00286/1.03392/4.93750 | 26.2 | 32.1 | 0.8 |
| **8** | 494.42 | 0.00160 | 3.5 | 0.3249 | 0.5302 | 0.00324/0.95000/5.09808 | 8.9 | 85 | 0.10 |

[a]Retention time is 10.4 ± 0.4 min at $\lambda_{max}$ = 275 ± 3 nm. [b]Retention time is 16.7 ± 0.5 min at $\lambda_{max}$ = 276 ± 3 nm.


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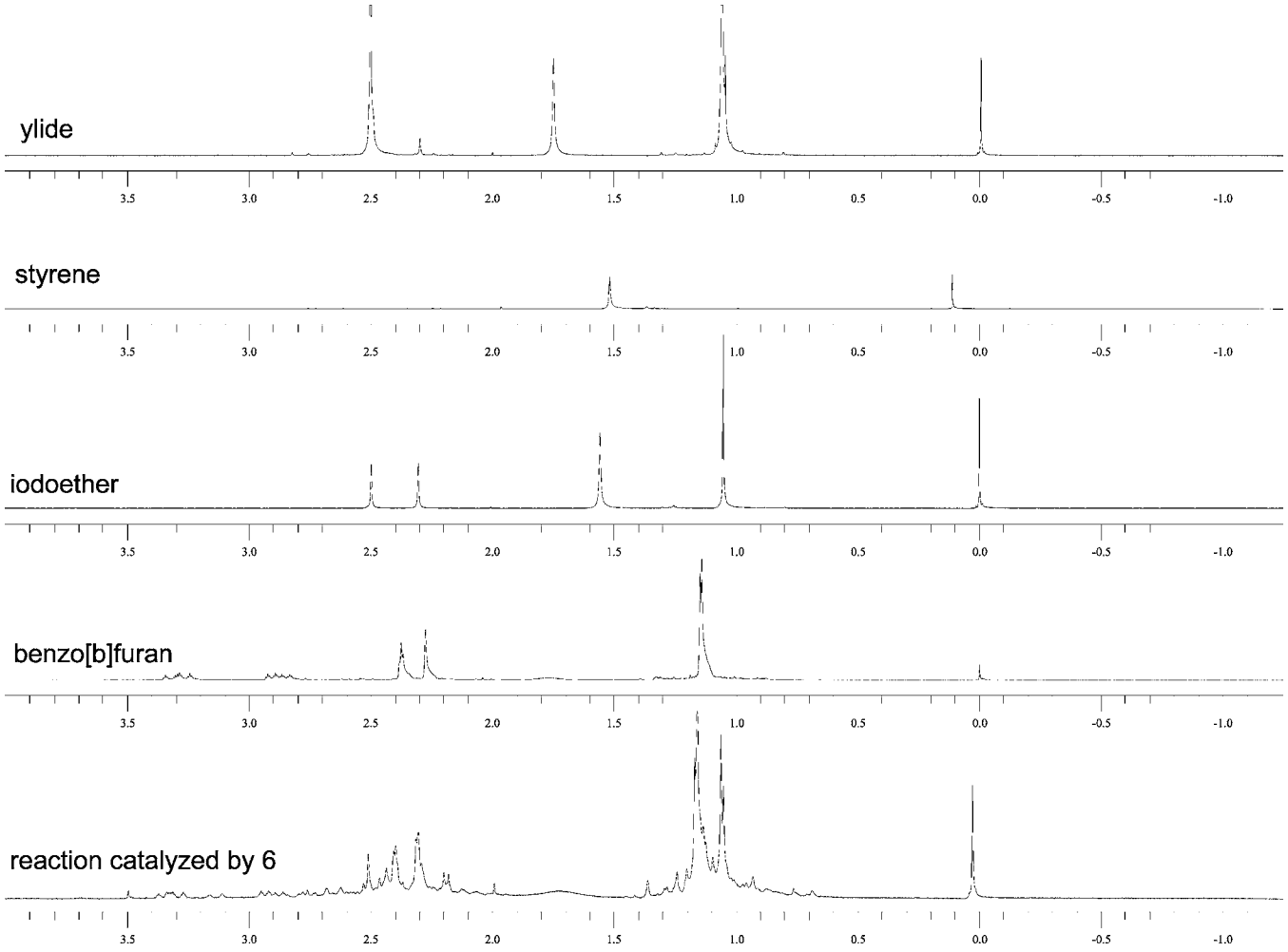


**Figure 4.** $^1$H NMR spectra of ylide, styrene, iodoether, benzo[*b*]furan, and the reaction mixture of ylide with styrene catalyzed by complex **6**.

**Table 3. Catalytic Activity of 4 upon the Reaction of Phenyliodonium Dimedonate, with Styrene, for the Formation of Heterocyclic Benzo[*b*]furans and Iodoether**

| amount of catalyst (mg) | ilidio/styrene (mg) | benzofuran retention time (min) | benzofuran area % | iodoether retention time (min) | iodoether area % | ratio B/I |
|---|---|---|---|---|---|---|
| 3.56 | 338.4/668.4 | 10.495 | 35.72 | 16.166 | 17.83 | 2.00 |
| 3.59 | 332.0/545.6 | 10.538 | 32.41 | 16.237 | 16.86 | 1.92 |
| 3.10 | 330.0/405.4 | 10.575 | 34.27 | 16.302 | 15.50 | 2.21 |
| 3.35 | 331.0/279.6 | 10.618 | 32.97 | 16.377 | 10.87 | 3.03 |
| 3.41 | 337.6/168.6 | 10.632 | 34.11 | 16.399 | 4.97 | 6.86 |
| 7.58 | 338.4/668.4 | 10.646 | 37.70 | 16.399 | 22.29 | 1.69 |
| 7.10 | 337.2/521.2 | 10.649 | 33.83 | 16.406 | 17.57 | 1.93 |
| 6.65 | 329.8/387.6 | 10.641 | 31.05 | 16.396 | 12.34 | 2.52 |
| 6.89 | 329.3/274.6 | 10.620 | 37.10 | 16.360 | 9.44 | 3.93 |
| 6.81 | 335.0/168.8 | 10.587 | 30.46 | 16.310 | 4.45 | 6.84 |
| 1.08 | 168.5/268.2 | 10.479 | 36.76 | 16.120 | 15.26 | 2.41 |
| 2.33 | 171.6/296.0 | 10.409 | 36.19 | 16.023 | 17.17 | 2.11 |
| 10.95 | 331.7/527.2 | 10.484 | 33.42 | 16.104 | 23.52 | 1.42 |

$TS_{1A}$ transition state (Figure 5). The calculated bond lengths of C−I and I−Ph were 2.083 and 2.121 Å, respectively. The required activation energy was estimated to 55.8 kcal mol$^{-1}$. A single imaginary frequency corresponding to the reaction coordinate of $TS_{1A}$ was calculated at 121*i* cm$^{-1}$ involving the C···I bond motion, as expected. The reaction involves a second transition state ($TS_{1B}$) where styrene attacks the cyclohexyl ion. The activation barrier for this step was estimated to 44.7 kcal mol$^{-1}$, and the single corresponding imaginary frequency was at 302*i* cm$^{-1}$. Significant intramolecular HOMO−LUMO interactions are evident (Figure 6) where the donor MOs are mainly $\pi$-type and localized on the ethenyl double bond while the acceptor MOs are mainly localized on the electrophilic carbon atom of the cyclohexyl ion. The rate determining step is the dissociation process of PhI, and this is probably the reason why extra energy


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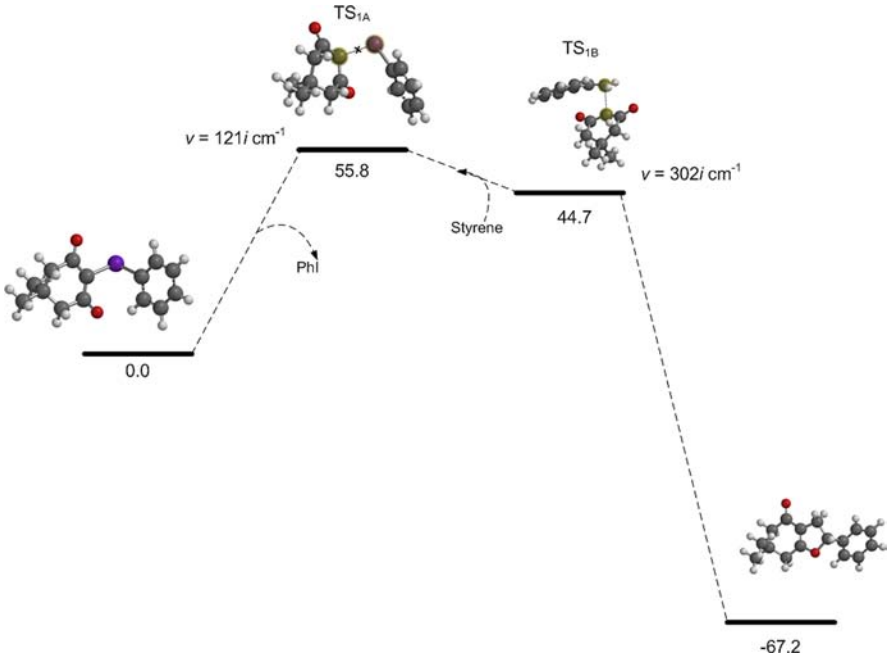


**Figure 5.** Potential energy (kcal mol$^{-1}$) reaction profiles for reaction 1.

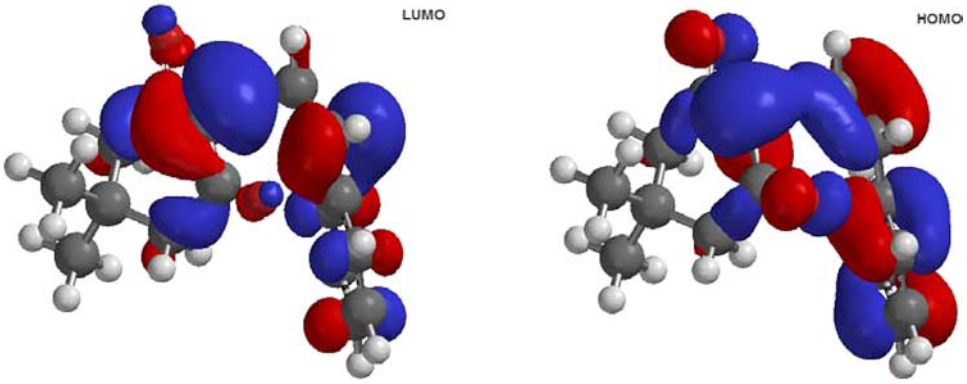


**Figure 6.** Frontier molecular orbitals of $TS_{1B}$.

(from irradiation) is needed to proceed with the formation of benzofuran. The whole process is strongly exergonic (the change in the Gibbs free energy is negative, indicating a spontaneous reaction), and the calculated energy was −67.2 kcal mol$^{-1}$. The uncatalyzed reaction toward 2-iodo-5,5-dimethyl-3-phenoxycyclohex-2-en-1-one (reaction 3) is a phenyl group migration similar to the one studied before[7a] with higher level calculations (B3LYP/6-311+G(d,p) ∪ SDD(I)). Our lower level calculations however, were also able to accurately reproduce the reaction scheme (Figure 7). The phenyl group migrates to quinonic oxygen via a single transition state ($TS_3$) requiring 37.3 kcal mol$^{-1}$ with only one imaginary frequency at 581*i* cm$^{-1}$. Therefore, gentle heating is required for this thermal transformation. The reaction is thermodynamically feasible since the calculated exergonicity was −45.9 kcal mol$^{-1}$.

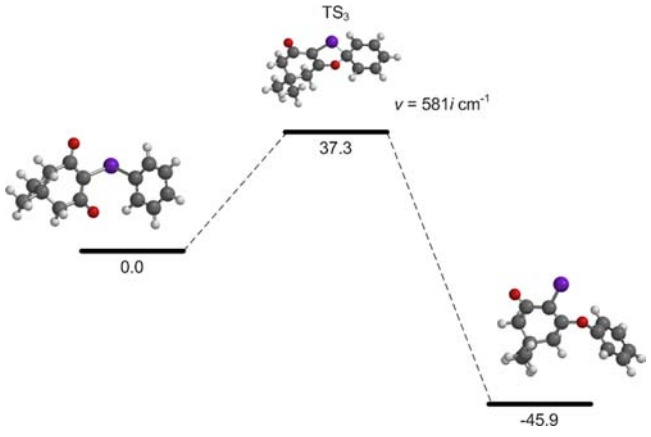


**Figure 7.** Potential energy (kcal mol$^{-1}$) reaction profiles for reaction 3 (phenyl group migration).

## CONCLUSIONS

Since benzofurans and their derivatives are either pharmaceutical agents or basic compounds precursors in the synthesis of important drugs, the development of novel synthetic routes for benzofurans such the reaction of phenyliodonium dimedonate with styrene, Scheme 1, was investigated since the late 1980s.[6] It has been reported that iodoether is isolated when the reaction is carryied out under reflux (Scheme 1 reaction 3), while benzofurnas are readily derived when the reaction is carrying out


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either under irradiation or in the presence of copper(II) acetate (Scheme 1 reactions 1, 2).

Our computational studies have shown that during the benzo[*b*]furan formation from the reaction of phenyliodonium dimedonate with styrene a dissociation of IPh is first occurring with simultaneous attack of styrene to the cyclohexyl ion via a Friedel−Crafts mechanism (Scheme 1; reactions 1, 2). Intramolecular HOMO−LUMO interactions are evident (Figure 6) where the donor MOs are mainly $\pi$-type and localized on the ethenyl double bond while the acceptor MOs are mainly localized on the electrophilic carbon atom of the cyclohexyl ion. The activation barrier for this step is estimated to 44.7 kcal. The rate determining step is the dissociation process of PhI, and this is probably the reason why extra energy from irradiation or lowering of the barrier from a catalyst, is needed to proceed with the formation of benzofuran. It is already reported that the conversion of iodonium ylides into other ylides, upon heating of their solution in the presence of various copper complexes or salts, is proceeded through the formation of carbenes,[17a] while the dissociation of PhI from phenyliodonium dimedonate to the corresponding carbene is also observed during their reaction of the iodonium ylide with iron(II)- or iron(III)-porphyrins,[17b] supporting further the mechanism concluded through this work.

The present study aims in the elucidation of the role of the catalyst and into the development of new complexes with higher catalytic activity for the reaction of phenyliodonium dimedonate with styrene toward benzofuran. Copper(I) chloride was previously used as catalyst for the intramolecular cyclization of aryl substituted iodonium ylides and for the regioselective cyclopropanation reactions using iodonium ylides for the synthesis of prostaglandin precursors with high success.[17c,d] The antithyroid drug 6-*n*-propylthiouracil (ptu) reacts with copper(I) iodide in the absence or presence of arylphosphines to form a complexes with planar trigonal or tetrahedral geometry around the metal ions. Copper iodide complexes often forms oligomers and polymers where the building blocks are catenated through iodo bridges. Structures of monomer copper(I) iodide complexes with thioamides having either trigonal or tetrahedral geometries are rare, and only seven trigonal[15] or five tetrahedral[8,16] such structures are known up to now.

It has been demonstrated here that copper(I) complexes **1**−**7** catalyze the formation of benzo[*b*]furan as well as copper(II) acetate,[6] indicating that the mechanism might not be a redox process. Also, copper(I) complexes (**1**−**7**) exhibit higher catalytic activity than the corresponding one of gold(I) (**8**). Moreover, both monomeric or dimeric copper(I) complexes with trigonal or tetrahedral geometry around the metal center exhibit strong catalytic activity. Iodo containing complexes **1**−**5** show better activity than the ones with chlorine (**6**−**8**). A synergistic effect of triphenystibine and iodide or thiarylphosphine and ptu ligands increases the catalytic ability of the complexes. Moreover, the amount of iodoether derived is significantly lower, while the amount of benzo[*b*]furan yielded remains unchanged by decreasing of the amount of styrene, with simultaneous maintaining constant amount of catalyst and ylide. Our work aims in the design and development of new efficient catalyst for benzofurans formation.

## EXPERIMENTAL SECTION

**Materials and Instruments.** All solvents used were reagent grade. Copper(I) iodide and chloride (Riedel-deHaen), triphenylphosphine, and tri(p-tolyl)phosphine (Merk) ligand (Aldrich-Merk) were used with no other purification prior to use. Melting points were measured in open tubes with a STUART scientific apparatus and are uncorrected. Infrared spectra in the region of 4000−370 $cm^{-1}$ were obtain in KBr discs while far-infrared spectra in the region of 400−50 $cm^{-1}$ were obtain in polyethylene discs, with a Perkin - Elmer Spectrum GX FT-IR spectrometer. A Jasco UV/vis/NIR V 570 series spectrophotometer was used to obtain the electronic absorption spectra.

**Synthesis and Crystallization of [CuI(ptu)$_2$](toluene) (1), [CuI(tpp)$_2$(ptu)] (2), [CuI(tptp)$_2$(ptu)] (3), [(tpSb)$_2$Cu($\mu_2$-I)$_2$Cu-(tpSb)$_2$] (4), [(tpp)Cu($\mu_2$-I)$_2$Cu(tpp)$_2$] (5), [(tpp)Cu($\mu_2$-Cl)$_2$Cu-(tpp)$_2$] (6), [CuCl(tpp)$_3$·(CH$_3$CN)] (7), and [AuCl(tpp)] (8) Complexes.** A suspension of 0.5 mmol CuI (0.085 gr) and 1 mmol 6-*n*-propylthiouracil (ptu) (0.130 gr) in toluene were stirred and headed under reflux. A clear solution was finally formed. The solution was then filter off, and the clear solution was kept in the darkness at room temperature (rt). After few days, a pale yellow crystal of complex **1** suitable for single crystal analysis by X-ray crystallography were grown, and they were collected. Complexes **2** and **3** were prepared as follows: 1 mmol triarylphosphine (0.262 g triphenylphosphine (**2**) and 0.304 g tri(*p*-tolyl)phosphine (**3**)), 0.5 mmol (0.065 g) 6-*n*-propylthiouracil (ptu) were suspended to 20 $cm^3$ methanol/acetonitrile solution (1:1) which contains 0.5 mmol of copper(I) iodide (0.085 g). The mixture was stirred and heated at 50 °C until a clear solution is formed. The clear solution was then filtered off and kept in the darkness at rt. After 24 h colorless crystals, of complexes (**2**, **3**), suitable for single crystal analysis by X-ray crystallography were filter off.

***1***. Pale yellow crystal, yield: 12%, decomposition point: 239−245 °C; IR ($cm^{-1}$), (KBr): 1641vs, 1552vs, 1438s, 1158s, 836m, 566s. UV−vis (DMSO) $\lambda_{max}$ (log $\varepsilon$): 276 nm (4.47). UV−vis ($CHCl_3$) $\lambda_{max}$ (log $\varepsilon$): 278 nm (4.32) (Supporting Information Figures S1, S6).

***2***. Pale yellow crystal, yield: 76%, decomposition point: 220−230 °C; IR ($cm^{-1}$), (KBr): 1675vs, 1541vs, 1434vs, 1158m, 741s, 695vs, 517s. $^1$H NMR-(DMSO-$d_6$) (ppm): 12.3 (br H(N) and 12.2 (br, H(N)), 7.4−7.3 (m, $H_{aromatic}$), 1.59−1.50 (q, *i*-pr- group), 1.24 (br, *i*-pr- group), 0.91−0.85 (t, *i*-pr- group). UV−vis (DMSO) $\lambda_{max}$ (log $\varepsilon$): 276 nm (4.47) (Supporting Information Figures S2, S4, S7).

***3***. Pale yellow crystal, yield: 56%, decomposition point: 175−180 °C; IR ($cm^{-1}$), (KBr): 1668vs, 1541vs, 1497s, 1442s, 1187vs, 705vs, 518vs $^1$H NMR -(DMSO-$d_6$) (ppm): 12.3 (br H(N) and 12.2 (br, H(N)), 7.2−7.1 (m, $H_{aromatic}$), 2.3 (s, *Methyl*- group), 1.6−1.5 (q, *i*-pr- group), 1.24 (br, *i*-pr- group), 0.91−0.85 (t, *i*-pr- group). UV−vis (DMSO) $\lambda_{max}$ (log $\varepsilon$): 276 nm (4.46) (Supporting Information Figures S3, S5, S8).

The synthesis and characterization of complexes **4**−**8** are already reported.[13,14] However, compounds **4** and **5** were prepared also here by a modified procedure as follows: a suspension of 1 mmol (0.353 g) triphenylantimony(III) (**4**) or 0.75 mmol (0.197 g) triphenylphosphine (**5**) and 0.5 mmol copper(I) iodide (0.085 g) in 20 $cm^3$ methanol/acetonitrile solution (1:1) was heated at 50 °C until the formation of a clear solution. The clear solution was then filtered off and kept in the darkness at rt. After 24 h, colorless crystals, of complexes **4** and **5**, suitable for single crystal analysis by X-ray crystallography were filtered off.

Complexes **6**−**8** were prepared according to the methods described in refs 13d and 14e. Their analytical and spectroscopic data were found to be identical to that already reported.

**X-ray Structure Determination.** Intensity data for the crystals of **1**−**3** and **5** were collected on an Oxford Diffraction CCD instrument while those of **1** were collected on a KUMA KM4CCD four-circle diffractometer, using graphite monochromated Mo radiation ($\lambda$ = 0.71073 Å). Cell parameters were determined by least-squares refinement of the diffraction data.[17a]

Data of **1**−**3** and **5** were corrected for Lorentz-polarization effects and absorption.[18] The structures were solved with direct methods with SHELXS97[19] and refined by full-matrix least-squares procedures on F2 with SHELXL97.[19] All non-hydrogen atoms were refined anisotropically, hydrogen atoms were located at calculated positions and refined via the "riding model" with isotropic thermal parameters fixed at 1.2 (1.3 for $CH_3$ groups) times the $U_{eq}$ value of the appropriate carrier atom. Significant crystal data are given in Table 4.

Supplementary data for complexes **1**−**5** are available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (E-mail: deposit@ccdc.cam.ac.uk),

**Table 4. Structure Refinement Details for the Complexes 1−5**

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| empirical formula | $C_{14}H_{20}CuIN_4O_2S_2$, $C_7H_8$ | $C_{43}H_{40}CuIN_2OP_2S$ | $C_{49}H_{52}CuIN_2OP_2S$ | $C_{72}H_{60}Cu_2I_2Sb_4$ | $C_{54}H_{45}Cu_2I_2P_3$ |
| formula weight | 623.06 | 885.23 | 969.39 | 1793.14 | 1167.71 |
| $T$ (K) | 100 | 100 | 100 | 293 | 100 |
| cryst syst | monoclinic | triclinic | triclinic | monoclinic | monoclinic |
| space group | $P2_1/c$ | $P\bar{1}$ | $P\bar{1}$ | $P2_1/c$ | $P2_1$ |
| $a$ (Å) | 13.1237(6) | 10.8524(4) | 11.5843(8) | 24.4463(6) | 10.3675(4) |
| $b$ (Å) | 22.6268(8) | 12.7124(5) | 14.6751(10) | 13.9088(3) | 20.5572(6) |
| $c$ (Å) | 8.3711(3) | 15.3797(5) | 15.0047(9) | 20.2168(5) | 11.7116(4) |
| $\alpha$ (deg) | 90 | 79.442(3) | 80.494(5) | 90 | 90 |
| $\beta$(deg) | 97.503(4) | 81.971(3) | 82.354(5) | 111.241(3) | 105.640(4) |
| $\gamma$(deg) | 90 | 69.267(4) | 72.311(6) | 90 | 90 |
| $V$ (Å$^3$) | 2464.49(17) | 1944.31(13) | 2387.5(3) | 6407.1(3) | 2403.64(15) |
| $Z$ | 4 | 2 | 2 | 4 | 2 |
| $\rho$calcd (g/cm$^3$) | 1.679 | 1.512 | 1.349 | 1.859 | 1.613 |
| $\mu$ (mm$^{-1}$) | 2.3 | 1.5 | 1.3 | 3.3 | 2.3 |
| $\theta_{min} < 2\theta < \theta_{max}$ | $3.6 < 2\theta < 25.0$ | $3.8 < 2\theta < 25.0$ | $2.9 < 2\theta < 25.0$ | $2.9 < 2\theta < 26.5$ | $2.8 < 2\theta < 26.5$ |
| data collected, uniq. data | 32191, 4320 | 26214, 6817 | 19368, 8388 | 53912, 12437 | 22356, 9541 |
| independent reflections ($R_{int}$) | 2729, (0.150) | 5827 (0.037) | 6524 (0.048) | 10239 (0.028) | 7625 (0.071) |
| R1, wR2 [$I > 2\sigma(I)$], S | 0.0622, 0.1565, 0.97 | 0.0272, 0.0631, 1.04 | 0.0816, 0.2437, 1.07 | 0.0220, 0.0480, 1.05 | 0.0488, 0.0723, 0.97 |

on request, quoting the deposition nos. CCDC-888395 (**1**), 888396 (**2**), 888397 (**3**), 889071 (**4**), and 888398 (**5**), respectively.

**Catalysis.** In an Erlenmeyer spherical flask the proper amount of ylide, styrene, and catalyst are added. The reaction mixture is refluxed under continuous stirring at 114−118 °C. A few seconds later, the solid ylide turned into a clear dark liquid and the refluxing is continued for 4 min more. The benzo[*b*]furan yielded was detected by the means of HPLC.

**HPLC Assay.** The sample constituents were isocratically separated using acetonitrile/water (55/45) with a flow rate of 1 mL/min, using a chromatographic system comprised of a Shimadzu liquid chromatograph equipped with two LC-8A solvent delivery pumps coupled to a communication bus module (CBM-20A) which was used to control sample injection (SIL-10AP autosampler). The peaks representing the sample constituents were recognized both by the retention time and their spectrum pattern recorded on a Shimadzu SPD-M20A Diode Array detector working under LC Solution v.1.2.3 chromatography software.

**Computational Details.** All calculations regarding reactants, transition states, and products were carried out using SPARTAN '08.[20] The equilibrium and transition gas-phase structures were fully optimized, without any geometry constraints, using ab initio calculations performed at the HF/3-21G* level. To characterize the nature of the stationary points, harmonic vibrational frequencies were calculated at the same level of theory. Only one negative Hessian element was found for each transition state while no negative eigenvalues were computed for reactants and products.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Figures S1−S8 and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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