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Well-Defined Ir/Pd Complexes with a Triazolyl-diylidene Bridge as Catalysts for Multiple Tandem Reactions

Alessandro Zanardi, José A. Mata, and Eduardo Peris*

Departamento de Química Inorgánica y Orgánica, Universitat Jaume I, Avda. Vicente Sos Baynat s/n, Castellón, E-12071 Spain

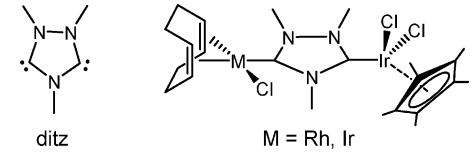
Received July 20, 2009; E-mail: eperis@qio.uji.es

Abstract: The ligand 1,2,4-trimethyl-triazolyl-diylidene has been used for the preparation of a series of three iridium/palladium heterometallic complexes that have been fully characterized. The presence of the two different metals allows tandem processes to be designed by combining reactions that are typically catalyzed by Ir and Pd. Three tandem reactions have been studied: dehalogenation/transfer hydrogenation of haloacetophenones, Suzuki-coupling/transfer hydrogenation of *p*-bromoacetophenone, and Suzuki-coupling/α-alkylation of *p*-bromoacetophenone. All three reactions yielded excellent outcomes to the corresponding final products, with the relevant feature that the heterodimetallic complexes are more active than the sum of the corresponding homodimetallic species. All three catalytic reactions reported here constitute unprecedented examples of tandem approaches to complex organic molecules.

Introduction

The recent interest in the development of one-pot multiple catalytic transformations is a consequence of the increasing demand for environmentally benign and economical synthetic processes.[1,2] Among these multiple catalytic transformations, those enclosed with the term "tandem" refer to coupled catalyses in which the sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes.[1,3] In a practical way, tandem catalyses allow reactions to be carried out in a single reaction vessel, with an important simplification of the reaction workups and minimum change in conditions. For the design of a tandem reaction, it is important to study the catalyst compatibility with the residual materials from the catalytic steps comprising the overall process. Basically, two different types of catalytic systems can be used in a tandem reaction: (i) a single catalyst performs the mechanistically distinct reactions of the tandem process or (ii) two (or more) different catalysts are added to the reaction medium to afford the two (or more) different transformations. Each of these two possibilities has a series of advantages and disadvantages. If we use a single catalyst, in the construction of the tandem sequence, we can only combine transformations for which this catalyst is active. Alternatively, we can use two different catalysts to increase the number of possible combinations, specially if we pretend to combine reactions that are fundamentally different in nature. This alternative obviously reduces the atomic economy of the reaction, specially if we take into account that the preparation of the two different catalysts requires double the amount of time, solvents, reagents, and purification and characterization procedures.

Scheme 1

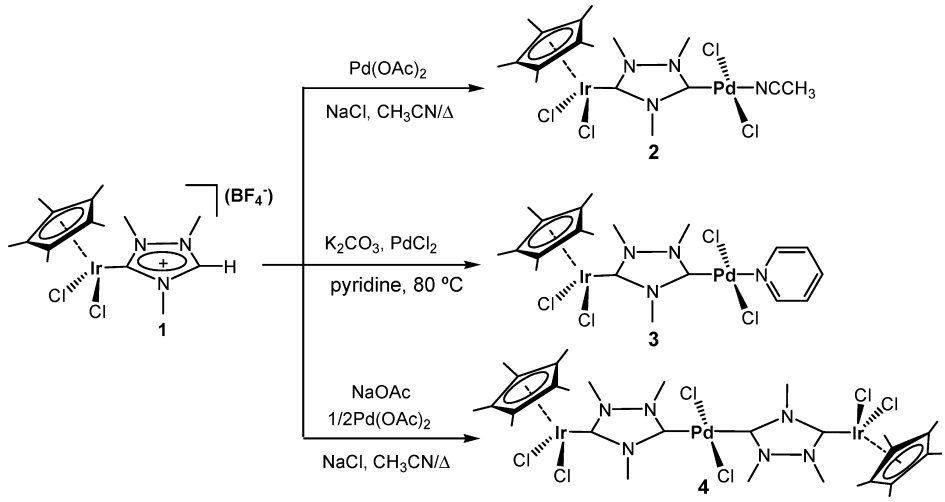


We have recently been interested in the preparation of stable catalysts that may be compatible with a wide variety of organic transformations.[4] In our search, we found that the 1,2,4-trimethyltriazolyl-diylidene ligand (ditz) provides a high versatility that makes it suitable for the coordination to different metals, such as Rh,[5,6] Ir,[5,6] Pd,[7] and Ru.[8] We also found that ditz was a useful synthon for the preparation of well-defined heterodimetallic complexes that may be applied for the design of tandem reactions. The first set of such complexes consisted of Rh^{I}/Ir^{III} and Ir^{I}/Ir^{III} species (Scheme 1) that we used in a tandem reaction implying the consecutive oxidative cyclization of 2-aminophenyl ethyl alcohol and the alkylation of the resulting indole with a series of primary alcohols.[6] Although these preliminary results were very promising, in the design of the mentioned tandem reaction, we found it difficult to combine catalytic reactions specifically promoted by Rh^{I} or Ir^{I} and Ir^{III}, due to their chemical similarities.

Aiming to search for a catalyst able to mediate two fundamentally different reactions, we now decided to extend the coordination of ditz to afford heterodimetallic species of Ir/Pd, so that in the design of the tandem reaction we can

(1) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754.
(2) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302.
(3) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.
(4) Corberan, R.; Mas-Marza, E.; Peris, E. *Eur. J. Inorg. Chem.* **2009**, 1700.
(5) Mas-Marza, E.; Mata, J. A.; Peris, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 3729.
(6) Zanardi, A.; Corberan, R.; Mata, J. A.; Peris, E. *Organometallics* **2008**, *27*, 3570.
(7) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 1480.
(8) Viciano, M.; Sanau, M.; Peris, E. *Organometallics* **2007**, *26*, 6050.

Scheme 2



combine the large and distinct library of transformations for which Ir and Pd precatalysts are potentially active. Following this idea, we have now prepared a series of Ir/Pd complexes that we have used in tandem reactions comprising different transformations of halo-acetophenones, typically catalyzed by Ir and Pd: (i) dehalogenation and transfer hydrogenation, (ii) Suzuki coupling and transfer hydrogenation, and (iii) Suzuki coupling and α-alkylation with primary alcohols.

Results and Discussion

Synthesis and Characterization of Compounds. The preparation of the heterodimetallic complexes of Ir/Pd was performed starting from the previously described compound **1**,[6] in which the azole ligand is acting as a monocarbene and still has a CH bond that can be activated to generate a second carbene. The reaction of **1** with $Pd(OAc)_2$ in refluxing CH_3CN in the presence of NaCl, affords compound **2** in high yield (68%). An analogue complex but with a pyridine instead of the acetonitrile ligand, can be obtained from the reaction of **1** and $PdCl_2$ in pyridine in the presence of K_2CO_3 (yield 78%). The trimetallic compound **4**, which contains two Ir-based fragments and one Pd, is prepared from the reaction between **1** and $Pd(OAc)_2$ (2:1) in refluxing acetonitrile in the presence of NaCl, although for this compound the yield was very low (13%). All of these reactions are summarized in Scheme 2. All three new complexes were characterized by NMR spectroscopy, electrospray mass spectrometry (ESI-MS), and elemental analysis.

The ^{1}H NMR spectrum of **2** shows three distinctive resonances due to the three methyl groups at the azole bridge, indicating the lack of symmetry. The more representative signals observed on the ^{13}C NMR spectrum are the ones assigned to the metalated carbenes, at δ 169.0 ($C_{carbene}$−Ir) and 158.7 ($C_{carbene}$−Pd). The dimetallic nature of the compound is confirmed by the data resulting from the electrospray mass spectrometry (ESI-MS), that shows a main peak at $m/z = 692.8$, due to $[M-Cl]^+$. Compound **3** also shows the three signals attributed to the methyl groups of the azole ring in the ^{1}HNMR spectrum, whereas the ^{13}C NMR spectrum shows the signals due to the two carbene carbons at 168.4 ($C_{carbene}$−Ir) and 163.4 ppm ($C_{carbene}$−Pd). The dimetallic nature of **3** is also confirmed by ESI-MS, with a peak at $m/z = 730.8$ assigned at $[M-Cl]^+$.

The ^{1}H NMR spectrum of the trimetallic complex **4** shows two resonances (2:1 integral ratio) due to the three methyl groups at the two azole bridges. According to the 2-fold symmetry of the molecule, three resonances should be expected, but two of them show accidental degeneracy. The compound was very insoluble in all ordinary deuterated solvents, so we could not get a proper ^{13}C NMR spectrum because concentrated solutions of **4** gave insoluble crystals after several minutes. The trimetallic nature of **4** was determined by ESI-MS, which showed peaks at $m/z = 1161.1$ and 562.1, due to $[M-Cl]^+$ and $[M-2Cl]^{2+}$, respectively. The complete determination of the structure of **4** was achieved by means of X-ray diffraction, as discussed in the following section.

X-ray Diffraction Studies. The molecular structures of **1**, **3**, and **4** were unambiguously determined by X-ray diffraction studies. Figures 1−3, show the ORTEP diagrams of **1**, **3**, and **4**, respectively. Compound **1** was crystallized as a PF_6^- salt after counterion exchange with KPF_6.

The molecular structure of **1** can be regarded as a three-legged piano-stool. Together with the triazolylidene, two chloro ligands and a Cp* ring complete the coordination sphere about the Ir center. The cationic nature of the complex is confirmed by the presence of a PF_6^- counterion. The Ir−$C_{carbene}$ distance is 2.048 Å, in the range of other analogue Cp*Ir(NHC) complexes,[9,10] and to a related complex in which the ditz ligand is bridging two Cp*Ir fragments (2.023 Å).[6]

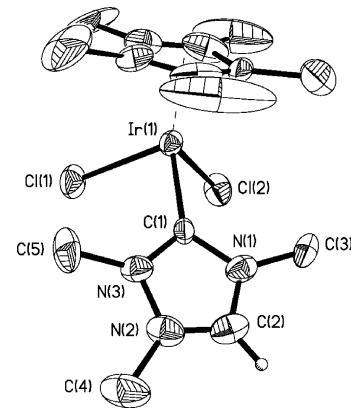


Figure 1. Molecular diagram of complex **1**. Ellipsoids at 50% probability level. Hydrogen atoms and counterion (PF_6^-) have been omitted for clarity. Selected bond lengths (Å) and angles (°): Ir(1)−C(1) 2.048(11), Ir(1)−Cl(1) 2.422(3), Ir(1)−Cl(2) 2.430(3), C(1)−Ir(1)−Cl(1) 90.0(3), Cl(1)−Ir(1)−Cl(2) 85.76(11), and C(1)−Ir(1)−Cl(2) 88.8(3).

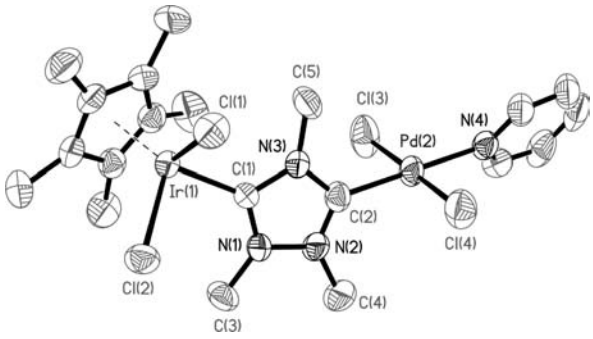


Figure 2. Molecular diagram of complex **3**. Ellipsoids at 50% probability level. Hydrogen atoms and solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (°): Ir(1)−C(1) 2.019(6), Ir(1)−Cl(1) 2.4256(17), Ir(1)−Cl(2) 2.4068(17), Pd(2)−C(2) 1.972(6), Pd(2)−Cl(3) 2.301(2), Pd(2)−Cl(4) 2.290(2), Pd(2)−N(4) 2.070(5), C(1)−Ir(1)−Cl(1) 90.31(17), C(1)−Ir(1)−Cl(2) 92.08(17), C(2)−Pd(2)−Cl(3) 87.2(2), and C(2)−Pd(2)−Cl(4) 91.2(2).

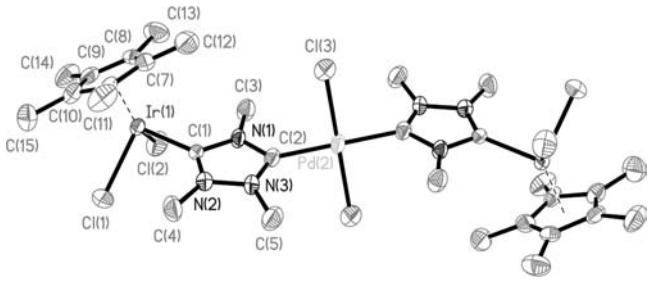
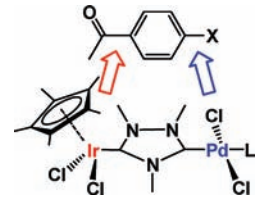


Figure 3. Molecular diagram of complex **4.** Ellipsoids at 50% probability level. Hydrogen atoms and solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (°): Ir(1)−C(1) 2.029(6), Ir(1)−Cl(1) 2.3959(18), Ir(1)−Cl(2) 2.4241(17), Pd(2)−C(2) 2.038(6), Pd(2)−Cl(3) 2.3159(18), C(1)−Ir(1)−Cl(1) 92.29(17), C(1)−Ir(1)−Cl(2) 92.23(17), and C(2)−Pd(2)−Cl(3) 88.96(17).

The molecular structure of compound **3** (Figure 2) consists of a Cp*$IrCl_2$ fragment connected to $PdCl_2Py$ by the triazolyl−diylidene ligand. The structure allows a comparison between the bond distances to Ir(III) and Pd(II) by the same ligand within the same compound. These distances are 2.019 and 1.972 Å for $Ir^{III}-C_{carbene}$ and $Pd^{II}-C_{carbene}$, respectively. The two chloro ligands on the Pd fragment adopt a trans configuration. The $Pd-N_{pyridine}$ distance is 2.070 Å, in the range of other similar bonds trans to NHCs,[11,12] and longer than those shown for other related complexes with non-NHC ligands,[13] indicating the high trans influence provided by the triazolylidene ligand. The Ir−Pd distance is 6.039 Å. The azole ring adopts an almost perpendicular orientation with respect to the coordination plane of the Pd fragment, according to the torsion angles Cl(3)−Pd(2)−C(2)−N(2) (95.95°) and Cl(4)−Pd(2)−C(2)−N(3) (98.54°).

The molecular structure of **4** can be regarded as two Cp*$IrCl_2$(triazolylidene) fragments connected by a *trans*-$PdCl_2$ bridge. The molecule shows an inversion center at the Pd atom, so the two Cp*$IrCl_2$ fragments are symmetry related. This makes the two azole rings to be essentially coplanar, with an anti configuration of the two Cp*Ir fragments along the Ir−Pd−Ir axis. The $Ir-C_{carbene}$ distance is 2.029 Å, similar to the same distance in other Cp*Ir fragments connected to ditz.[6] The Pd(2)−C(2) distance is 2.030 Å, longer than the distances shown for other previously reported Pd(II) complexes bound to ditz,[7,12] and to the Pd(2)−C(2) distance shown by compound **3** (1.972 Å), probably due to the mutually trans influence produced by the two triazolylidene ligands in **4**. The intermetallic distances in the molecule are 6.115 (Pd−Ir) and 12.229 Å (Ir−Ir). The azole rings deviate from the coordination plane of the Pd(II) fragment, as seen from the torsion angles of N(3)−C(2)−Pd(2)−Cl(3) (66.88°) and N(1)−C(2)−Pd(2)−Cl(3′) (61.75°).

Scheme 3



Catalytic Studies. Compounds **2**, **3**, and **4** offer an excellent opportunity to study concatenated catalytic transformations that imply the simultaneous activity of Ir and Pd precatalysts. Also, the fact that these catalysts present well-defined structures with a fixed and well determined ligand/metal ratio, circumvents the problems derived from the drawbacks attributed with in situ generated catalytic systems, mainly associated with phosphine-based catalysts.

Aiming to search for combinations of distinctive catalytic sequences promoted by Pd and Ir compounds, we decided to use halo-acetophenones as convenient starting substrates. We thought that these substrates may be of great utility because they combine a halide-aryl bond, for which Pd catalysts may provide a large library of transformations, and a C=O bond, for which Ir can afford a variety of reactions, mainly implying borrowing-hydrogen processes.[14−16]

(a) Dehalogenation/Transfer Hydrogenation of Halo-Acetophenones. The dehalogenation of aryl-halides represents an important transformation in organic synthesis,[17] with special interest in environmental remediation taking into account the high toxicity of polychlorinated arenes.[18] Pd-catalyzed dehalogenations of aryl-halides can take place in *i*PrOH in the presence of a strong base,[19] such as NaOtBu, the same reaction medium

(9) Corberan, R.; Sanau, M.; Peris, E. *Organometallics* **2006**, *25*, 4002. Corberan, R.; Sanau, M.; Peris, E. *Organometallics* **2007**, *26*, 3492.
(10) Corberan, R.; Sanau, M.; Peris, E. *J. Am. Chem. Soc.* **2006**, *128*, 3974. Corberan, R.; Lillo, V.; Mata, J. A.; Fernandez, E.; Peris, E. *Organometallics* **2007**, *26*, 4350. Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2005**, *24*, 3422.
(11) Dash, C.; Shaikh, M. M.; Ghosh, P. *Eur. J. Inorg. Chem.* **2009**, 1608.
(12) Zanardi, A.; Mata, J. A.; Peris, E. *Organometallics* **2009**, *28*, 4335.
(13) Jaganyi, D.; Tiba, F.; Munro, O. Q.; Petrovic, B.; Bugarcic, Z. D. *Dalton Trans.* **2006**, 2943. Bugarcic, Z. D.; Petrovic, B.; Zangrando, E. *Inorg. Chim. Acta* **2004**, *357*, 2650. Liu, Q. D.; Thorne, L.; Kozin, I.; Song, D. T.; Seward, C.; D'Iorio, M.; Tao, Y.; Wang, S. N. *J. Chem. Soc.-Dalton Trans.* **2002**, 3234.
(14) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D *Chem. Commun.* **2004**, 90.
(15) Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *4*, 116. Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, 4367. Hamid, M.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.
(16) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.
(17) Terstiege, I.; Maleczka, R. E. *J. Org. Chem.* **1999**, *64*, 342. Dorman, G.; Olszewski, J. D.; Prestwich, G. D.; Hong, Y.; Ahern, D. G. *J. Org. Chem.* **1995**, *60*, 2292. Parry, R. J.; Li, Y.; Gomez, E. E. *J. Am. Chem. Soc.* **1992**, *114*, 5946. Pinder, A. R. *Synthesis-Stuttgart* **1980**, 425.
(18) Morra, M. J.; Borek, V.; Koolpe, J. *J. Environ. Qual.* **2000**, *29*, 706.
(19) Navarro, O.; Marion, N.; Oonishi, Y.; Kelly, R. A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685.

Scheme 4

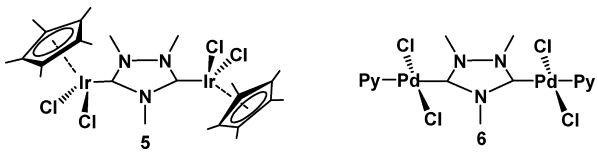
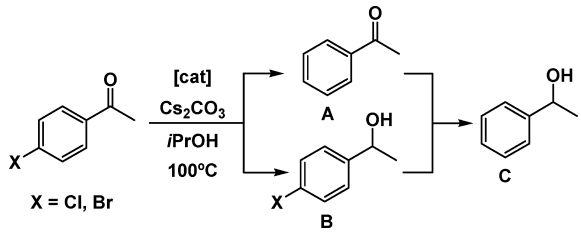


Table 1. Tandem Dehalogenation/Transfer Hydrogenation of Haloacetophenones[a]



entry	catalyst	X	time (h)	A (%)[b]	B (%)[b]	C (%)[b]
1	**2**	Br	20	22	0	75
2	**3**	Br	20	0	0	>99
3	**4**	Br	20	0	0	95
4	**5**	Br	20	0	89	0
5	**6**	Br	20	95	0	0
6	**5** + **6**[c]	Br	20	72	0	25
7	**3**	Br	9	21	1	77
8	**3**	Cl	25	3	12	83
9	**3**	Cl	9	21	42	34

[a] Reaction conditions: 4-haloacetophenone (0.36 mmol), Cs_2CO_3 (0.43 mmol), anisole as internal reference (0.36 mmol), catalyst (2 mol %) and 2 mL of 2-propanol. The solution was heated to 100 °C in aerobic conditions. [b] Yields determined by GC chromatography. [c] 1 mol % of **5** + 1 mol % of **6**.

that is often required for the transfer hydrogenation to ketones. With this in mind, and considering the activity shown by some Pd-NHC[19,20] and Cp*Ir(NHC)[4,9,21] complexes in each of these two processes, we decided to study the one-pot dehalogenation/transfer hydrogenation of haloacetophenones in iPrOH in basic medium. For comparative purposes, we also used the homodimetallic compounds **5**[6] and **6**[12] in this catalytic process (Scheme 4).

Table 1 summarizes the most representative data that we obtained for the tandem reaction under study. A first catalyst screening was performed in order to check which of the compounds tested afforded the best performances. For the reaction with *p*-bromoacetophenone, in *i*PrOH in the presence of Cs_2CO_3, compound **3** was the one to give the best catalytic outcomes (Table 1, entry 2), when comparing the yields to the final product C. The homodimetallic complexes of Ir (**5**) and Pd (**6**) showed activities only in the reactions for which these two complexes were expected to be active; that is, the Ir complex produced only the hydrogenation transfer product (B, entry 4), whereas the Pd compound gave only the dehalogenation process (A, entry 5). At a first glance this result may seem obvious, but we have to take into account that Fujita and Yamaguchi showed that $[Cp^*RhCl_2]_2$ is an effective catalyst in the dehalogenation of aryl chlorides,[22] so we could not discard

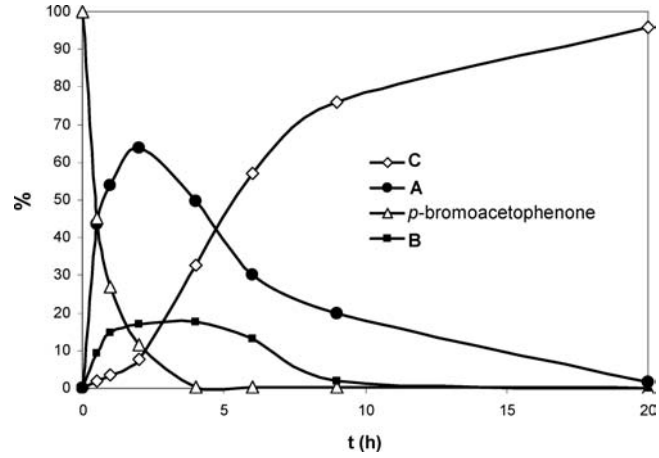


Figure 4. Time course of the transformation of *p*-bromoacetophenone with **3** (*i*PrOH, 100 °C, cat. = 2 mol %).

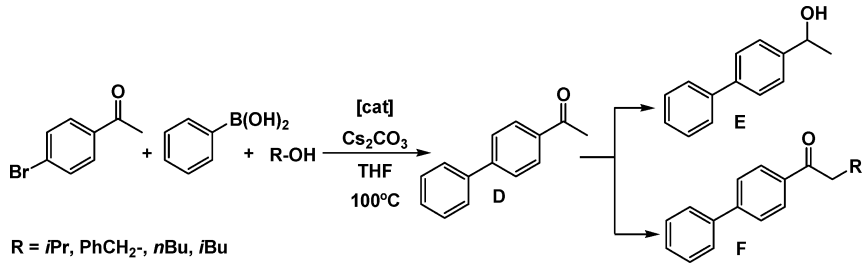
that the same reaction may have been catalyzed by the Ir complex **5**. Interestingly, addition of the two homodimetallic species **5** and **6** resulted in a much more ineffective catalytic system than any of the other three heterodimetallic species used (entry 6). This result suggests that some catalytic cooperativity between the two metals of the heterodimetallic species may be playing a role in the overall catalytic cycle, since the better activity of the well-defined heterodimetallic species is redundant in this and other related examples studied by us.[6,12] Also, in a parallel experiment, we studied the stability of **2**−**4**, by dissolving them in *i*PrOH and heating the solutions at 100 °C. The NMR spectra of the resulting solutions did not show any decomposition after 5 h, and only after 20 h could a small amount of unidentified decomposition products (<15%) be observed. This experiment was intended to disprove that the heterometallic species could evolve to a mixture of the two homodimetallic compounds (**5** and **6**) under the reaction conditions used in the catalytic assays. Under the same conditions (*i*PrOH, 100 °C) an equimolecular mixture of **5** and **6** resulted in the partial decomposition of the palladium complex **6**, as seen by NMR spectroscopy and by the deposition of some Pd-black in the reaction vessel.

Interestingly, the reaction is very clean, and we did not observe the formation of any other products apart from A, B, and C. This gave us a very good opportunity to study the reaction time course. Figure 4 shows the evolution of the reaction of *p*-bromoacetophenone using catalyst **3**. As can be seen, both the dehalogenation and transfer hydrogenation are simultaneous processes that afford the two reaction intermediates A and B, although the debromination is faster as seen by the formation of acetophenone (A) in a maximum yield of 65% after 2.5 h of reaction (the maximum yield for B is 17%). The formation of the 1-phenylethanol, C, is gradual, although a clear acceleration of the reaction is observed after 2.5 h, at the point where the maximum amount of A has been produced, suggesting that the transfer hydrogenation is faster for acetophenone than for *p*-bromoacetophenone, in agreement with previously published results.[23]

(b) Suzuki Coupling of *p*-Bromoacetophenone in the Presence of Different Alcohols. Given the activity shown by catalysts **2**, **3**, and **4** in the dehalogenation/transfer hydrogenation

(20) Viciu, M. S.; Grasa, G. A.; Nolan, S. P. *Organometallics* **2001**, *20*, 3607.
(21) da Costa, A. P.; Viciano, M.; Sanau, M.; Merino, S.; Tejeda, J.; Peris, E.; Royo, B. *Organometallics* **2008**, *27*, 1305. Hanasaka, F.; Tanabe, Y.; Fujita, K.; Yamaguchi, R. *Organometallics* **2006**, *25*, 826. Hanasaka, F.; Fujita, K. I.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490.
(22) Fujita, K.; Owaki, M.; Yamaguchi, R. *Chem. Commun.* **2002**, 2964.
(23) Cuervo, D.; Gamasa, M. P.; Gimeno, J. *Chem.—Eur. J.* **2004**, *10*, 425.

Table 2. Suzuki Coupling of *p*-Bromoacetophenone in the Presence of Alcohols[a]



entry	catalyst	time (h)	R−OH	**D** (%)[b]	**E** (%)[b]	**F** (%)[b]
1	**3**	4	*i*PrOH	58	28	0
2	**3**	7	*i*PrOH	2	88	0
3	**3**	0.5	$PhCH_2OH$	93	1	3
4	**3**	20	$PhCH_2OH$	5	1	80 (72)
5	**3**	0.5	*n*BuOH	94	0	4
6	**3**	20	*n*BuOH	4	2	92 (86)
7	**3**	0.5	*i*BuOH	96	1	1
8	**3**	20	*i*BuOH	7	3	77 (69)
9	**5** + **6**[c]	4	*i*PrOH	55	5	0
10	**5** + **6**[c]	20	*n*BuOH	21	13	29

[a] Reaction Conditions: 4-bromoacetophenone (0.36 mmol), phenylboronic acid (0.55 mmol), Cs_2CO_3 (1.08 mmol), anisole as internal reference (0.36 mmol), catalyst (2 mol %), 2 mL of R−OH and 2 mL THF. The solution was heated to 100 °C. [b] Yields determined by GC chromatography (isolated yields in parentheses). Less than 8% (based on $Ph-B(OH)_2$) of Ph−Ph formed. [c] 1 mol % of **5** + 1 mol % of **6**.

of haloacetophenones, we decided to extend the catalytic studies to see if other related transformations could be coupled. Nolan and co-workers recently showed that the catalytic dehalogenation and the Suzuki−Miyaura reaction are intertwined, sharing the oxidative addition step.[19] Also, many transfer hydrogenation catalysts are active in a variety of "hydrogen-borrowing" processes. Among all hydrogen-borrowing processes,[14] those imploying the formation of C−C bonds such as the α-alkylation of ketones with primary alcohols[16,24] constitute valuable examples of environmental friendly processes that facilitate the formation of complex organic structures. We also took into account that both processes (the Suzuki-Miyaura coupling and the α-alkylation of ketones) are usually performed in the presence of alcohols and in basic medium; therefore, the a priori chances of compatibility are high. Based on these, we decided to combine two C−C coupling reactions typically catalyzed for palladium and iridium. For this catalytic study, we only used compound **3**, because it showed the best outcomes compared to those studied in the dehalogenation/transfer hydrogenation process described above (Table 1). This model reaction has straightforward application, because the resulting biphenyl substituted ketones are known to behave as non steroidal inhibitors of 5α-reductase, the enzyme that catalyzes the conversion of testosterone to dihydrotestosterone.[25]

Table 2 shows the most representative data for the Suzuki coupling of *p*-bromoacetophenone in the presence of secondary and primary alcohols. The reactions were performed using a 2 mol % catalyst loading, at 100 °C in a sealed tube containing a solution of the substrate in 1:1 mixtures of THF and alcohol. As seen from the results shown, the Suzuki C−C coupling reaction is fast, affording almost quantitative yields on the formation of **D** after 0.5 h. The Ir-catalyzed process needs longer reaction times, and it can be directed toward the transfer hydrogenation product **E**, when the secondary alcohol (*i*PrOH) is used, or to the α-alkylated ketone (**F**), for the reactions performed in the presence of primary alcohols (benzyl alcohol, *n*BuOH and *i*BuOH). For all four reactions studied the process afforded very high yields (80−90%) on either of the reaction products (Table 2, entries 2, 4, 6, and 8), a result that is even more remarkable if we take into account that the overall yields are due to a combination of inherently distinct catalytic processes. As minor byproducts (less than 8%), small amounts of biphenyl were formed, due to the coupling of phenylboronic acid. Again, mixtures of **5** and **6** were tested in order to compare their activity with that shown by **3**. As seen from the data shown in Table 2 (entries 9 and 10), the mixture of the two homodimetallic compounds display lower activity than that shown by **3**, proving one more time the better activity of the well-defined heterodimetallic species.

Interestingly, the reaction is carried out in the presence of a weak base (Cs_2CO_3), instead of the strong bases that are often needed for the activation of both C−C coupling processes. It is also important to point out that, apart from the base, no further additives are needed for the activation of the catalyst, thus reducing the presence of undesired contaminating species that can interfere in either of the catalytic steps of the overall process and also reduce the atomic economy of the reaction.

Conclusions

In this work we prepared a set of three different heterometallic complexes of Ir/Pd, in which the metals are connected through a triazolyl-diylidene ligand. These complexes proved to be active catalysts in three different tandem processes, namely the dehalogenation/transfer hydrogenation of haloacetophenones, Suzuki-coupling/transfer hydrogenation of *p*-bromoacetophenone, and Suzuki-coupling/α-alkylation of *p*-bromoacetophenone. The selection of the tandem reaction is performed by very small changes in the reaction conditions that are directing the reaction to one of the three possible reaction products. All of these tandem reactions are valuable catalytic transformations that have not been reported before and constitute a clear advance over the synthetic procedures to the same final products that

(24) Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988.
(25) McCarthy, A. R.; Hartmann, R. W.; Abell, A. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3603. Picard, F.; Schulz, T.; Hartmann, R. W. *Bioorg. Med. Chem.* **2002**, *10*, 437.

would imply the use of two different catalysts and complicated workups requiring the isolation of all reaction intermediates. Connected to this point, the fact that the use of a single well-defined catalyst (either **2**, **3**, or **4**) yields a better catalytic outcome than a mixture of two homodimetallic compounds (**5** + **6**) results in a clear benefit provided by the heterometallic species, not only because it affords a more atom-efficient process, but because it also suggests that the heterometallic species can improve its catalytic outcome due to catalytic cooperativity or, at least, it avoids any interference between the two active metal fragments (an alternative possible explanation to the poorer outcome shown by the mixture of catalysts).

All three tandem reactions reported here constitute efficient methods for the generation of complex organic molecules by one-pot procedures, combining two different processes typically catalyzed by distinct metal complexes. Among the examples reported here, the one-pot preparation of biphenyl-substituted ketones, provides a much easier route to species with potential pharmaceutical applications.[25] The three model reactions are obviously just the tip of the iceberg if we consider the number of possible combinations of catalytic transformations that we can carry out starting from these simple and easy-to-make Ir−Pd species. This number is even larger if we consider the variety of heterodimetallic complexes that can be obtained from triazolylidene ligands.

Experimental Section

General Procedures. Compounds **1**,[6] **5**,[6] and **6**[12] were prepared according to literature procedures. All other reagents and solvents were used as received from commercial suppliers. Synthesis and catalytic experiments were carried out under aerobic conditions and without solvent pretreatment. NMR spectra were recorded on Varian spectrometers operating at 300 or 500 MHz (^{1}H NMR) and 75 and 125 MHz (^{13}C NMR), respectively, and referenced to $SiMe_4$ (δ in ppm and J in Hertz). NMR spectra were recorded at room temperature with $CDCl_3$ unless otherwise stated. A QTOF I (quadrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface (Micromass, Manchester, UK) was used. The drying gas as well as nebulizing gas was nitrogen at a flow of 400 L/h and 80 L/h respectively. The temperature of the source block was set to 120 °C and the desolvation temperature to 150 °C. A capillary voltage of 3.5 KV was used in the positive scan mode, and the cone voltage was set to 30 V. Mass calibration was performed using a solution of sodium iodide in isopropanol: water (50:50) from m/z 150 to 1000 amu. Sample solutions (aprox 1×10^{-4} M) in dichlormethane:methanol (50:50) were infused via a syringe pump directly connected to the interface at a flow of 10 μL/min. A 1 μg/mL solution of 3,5-diiodo-L-tyrosine was used as a lock mass. Elemental analyses were carried out on a EuroEA3000 Eurovector Analyzer. A gas chromatograph GC-2010 (Shimadzu) equipped with a FID and a Teknokroma (TRB-5MS, 30m × 0.25 mm × 0.25 μm) column and Gas chromatograph/Mass spectrometer GCMS-QP2010 (Shimadzu) equipped with a Teknokroma (TRB-5MS, 30m × 0.25 mm × 0.25 μm) column were used.

Synthesis of 2. A mixture of compound **1** (68 mg, 0.11 mmol), $Pd(OAc)_2$ (30 mg, 0.12 mmol), and sodium chloride (30 mg, 0.52 mmol) was refluxed overnight in CH_3CN. The reaction mixture was filtered through Celite, and the volatiles were removed under vacuum. The crude was dissolved in CH_2Cl_2 and purified by column chromatography. The pure compound **2** was eluted with dichloromethane/methanol (10:1) and precipitated from a mixture of acetone/diethylether to give a pale yellow solid. Yield 60 mg (68%). ^{1}H NMR (300 MHz, CD_3CN): δ 4.45 (s, 3H, NCH_3), 4.37 (s, 3H, NCH_3), 4.27 (s, 3H, NCH_3), 1.58 (s, 15H, C_5(CH_3)$_5$), (CH_3CN) not observed. ^{13}C NMR (125 MHz, CD_3CN): δ 169.0 ($C_{carbene}$ - Ir), 158.7 ($C_{carbene}$ - Pd), 91.1 (C_5(CH$_3$)$_5$), 41.1 (NCH$_3$), 38.3 (NCH$_3$), 38.1 (NCH$_3$), 8.8 (C_5(CH$_3$)$_5$). Anal. Calcd. For $C_{17}H_{27}Cl_4N_4IrPd$ (727.9): C, 28.05; H, 3.74; N, 7.70. Found: C, 28.24; H, 3.78; N, 7.95. Electrospray MS. Cone 20 V. (m/z, fragment): (692.8, [M-Cl]$^+$). ESI-TOF-MS (positive mode): monoisotopic peak 692.9963; calc. 692.9935. ε_r = 4.0 ppm.

Synthesis of 3. A mixture of compound **1** (100 mg, 0.17 mmol), $PdCl_2$ (36 mg, 0.2 mmol), and K_2CO_3 (70 mg, 0.5 mmol) was heated overnight in pyridine (3 mL) at 80 °C. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. Pure compound **3** was obtained as a light yellow solid after precipitation in dichloromethane/n-hexanes. Yield: 102 mg (78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.0 (d, $^3J_{H-H}$ = 5.5 Hz, 2H, Py), 7.87 (t, $^3J_{H-H}$ = 7.0 Hz, 1H, Py), 7.45 (t, $^3J_{H-H}$ = 6.5 Hz, 2H, Py), 4.60 (s, 3H, NCH_3), 4.58 (s, 3H, NCH_3), 4.41 (s, 3H, NCH_3), 1.73 (s, 15H, C_5(CH_3)$_5$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4 ($C_{carbene}$ - Ir), 163.4 ($C_{carbene}$ - Pd), 151.3, 151.1, 138, 124.9, 124.6 (Py), 90.6 (C_5(CH$_3$)$_5$), 40.7 (NCH$_3$), 38.1 (NCH$_3$), 37.5 (NCH$_3$), 9.0 (C_5(CH$_3$)$_5$). Anal. Calcd. For $C_{20}H_{29}Cl_4N_4IrPd$ (765.9): C, 31.36; H, 3.82; N, 7.31. Found: C, 31.77; H, 3.88; N, 7.35. Electrospray MS. Cone 5 V. (m/z, fragment): (730.8, [M-Cl]$^+$). ESI-TOF-MS (positive mode): monoisotopic peak 731.0101; calc. 731.0106. ε_r = 0.7 ppm.

Synthesis of 4. A mixture of compound **1** (160 mg, 0.27 mmol), $Pd(OAc)_2$ (28 mg, 0.11 mmol), sodium acetate (12 mg, 0.14 mmol), and sodium chloride (78 mg, 1.35 mmol) was refluxed overnight in CH_3CN. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum. The crude was dissolved in CH_2Cl_2 and purified by column chromatography. The pure compound **4** was eluted with acetone/dichloromethane (7:3). Yield 40 mg (13%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.46 (s, 12H, NCH_3), 4.31 (s, 6H, NCH_3), 1.65 (s, 30H, C_5(CH_3)$_5$). Anal. Calcd. For $C_{30}H_{48}Cl_6N_6Ir_2Pd$ (1196.3): C, 30.12; H, 4.04; N, 7.02. Found: C, 30.35; H, 4.19; N, 7.08. Electrospray MS. Cone 5 V. (m/z, fragment): (1161.1, [M-Cl]$^+$) and (562.1, [M-2Cl]$^{2+}$). ESI-TOF-MS (positive mode): monoisotopic peak 563.0481; calc. 563.0477. ε_r = 0.7 ppm.

Catalytic Studies. Dehalogenation/Transfer Hydrogenation of Halo-Acetophenones. In a typical run a capped vessel containing a stirrer bar was charged with the corresponding 4-haloacetophenone (0.36 mmol), Cs_2CO_3 (0.43 mmol), anisole as internal reference (0.36 mmol), catalyst (2 mol %), and 2 mL of 2-propanol. The reaction mixture was stirred at 100 °C for the appropriate time. Reaction monitoring, yields, and conversions were determined by GC chromatography. Products and intermediates were characterized by GC/MS. Isolated products were characterized by ^{1}H NMR and ^{13}C NMR after column chromatography purification using n-hexanes/ethylacetate (9:1).

Suzuki−Miyaura Coupling/Transfer Hydrogenation or α-Alkylation of Ketones. A capped vessel containing a stirrer bar was charged with 4-bromoacetophenone (0.36 mmol), phenylboronic acid (0.55 mmol), Cs_2CO_3 (1.08 mmol), anisole as internal reference (0.36 mmol), catalyst **3** (2 mol %), 2 mL of alcohol, and 2 mL of THF. The solution was heated to 100 °C for the appropriate time. The resulting products were characterized by comparing the spectroscopic data of the isolated compounds with those reported in the literature.[26]

NMR Characterization of F (R = nBu). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, Ph), 7.70 - 7.62 (m, 4H, Ph), 7.48 - 7.40 (m, 3H, Ph), 2.99 (t, $^3J_{H-H}$ = 8.9 Hz, 2H, CH$_2$), 1.80 - 1.76 (m, 2H, CH$_2$), 1.42 - 1.38 (m, 4H, CH$_2$), 0.94 (t, $^3J_{H-H}$ = 6.9 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4 (CO), 145.8, 140.2, 136.1 (C_q), 129.2, 128.9, 128.4, 127.5, 127.4 (CH), 38.9, 31.2, 24.4, 22.8 (CH$_2$), 14.2 (CH$_3$).

NMR characterization of F (R = CH$_2$Ph). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ph), 7.68 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, Ph), 7.63 (d, $^3J_{H-H}$ = 7.4 Hz, 2H, Ph), 7.49 - 7.44 (m, 4H,

(26) Mohrbacher, R. J.; Cromwell, N. H. *J. Am. Chem. Soc.* **1957**, *79*, 401. Henze, H. R.; Long, L. M. *J. Am. Chem. Soc.* **1941**, *63*, 1941. Long, L. M.; Henze, H. R. *J. Am. Chem. Soc.* **1941**, *63*, 1939.

Table 3. Crystallographic Data and Structure Refinement for Complexes **1**, **3**, and **4**[a]

	1	**3**	**4**
empirical formula	$C_{15}H_{25}Cl_2F_6IrN_3P$	$C_{46}H_{64}Cl_{25}Ir_2Pd_2N_8$	$C_{32}H_{52}Cl_{10}Ir_2PdN_6$
mol wt	655.45	2212.5	1366.1
radiation		Mo Kα (monochr); 0.71073 λ (Å)	
T (K)	293	273	293
cryst syst	monoclinic	monoclinic	monoclinic
space group	P2(1)	*C*2/*c*	P2(1)/c
a (Å)	9.1008(10)	28.9630(8)	8.6071(5)
b (Å)	8.8050(10)	13.9348(4)	17.8320(9)
c (Å)	14.0629(15)	23.0014(7)	14.8374(7)
α (deg)	90	90	90
β (deg)	105.996(2)	126.6400(10)	99.2250(10)
γ (deg)	90	90	90
V (Å^3)	1083.3(2)	7448.9(4)	2247.8(2)
Z	2	4	2
D_{calcd} (Mg m^{-3})	2.009	1.973	2.018
μ (Mo Kα) (mm^{-1})	6.540	4.972	6.927
total, unique no. of rflns	4984, 4176	10233, 8493	15388,5166
R_{int}	0.0501	0.0485	0.0596
no. of params, restrictions	259, 1	381, 0	238, 0
R, R_w ($I > 2\sigma$)	0.0438, 0.0573	0.0485, 0.0628	0.0373, 0.0697
GOF	1.008	1.039	1.022
min, max resid dens (e Å^{-3})	−1.303, 2.696	−1.357, 2.026	−0.84, 1.58

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, for all $I > 3\sigma(I)$. [b] $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2] > 1/2$.

Ph), 7.34 - 7.28 (m, 4H, Ph), 3.35 (t, $^3J_{H-H} = 6.8$ Hz, 2H, CH_2), 3.12 (t, $^3J_{H-H} = 7.6$ Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0 (CO), 145.9, 141.5, 130.1, 135.8 (C_q), 129.2, 128.9, 128.8, 128.6, 128.4, 127.5, 127.4, 126.4 (CH), 40.7, 30.5 (CH_2).

NMR characterization of F (R = *i*Bu). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, $^3J_{H-H} = 8.5$ Hz, 2H, Ph), 7.68 (d, $^3J_{H-H} = 8.5$ Hz, 2H, Ph), 7.62 (d, $^3J_{H-H} = 7.5$ Hz, 2H, Ph), 7.48 - 7.42 (m, 3H, Ph), 2.99 (t, $^3J_{H-H} = 7.3$ Hz, 2H, CH_2), 1.80 - 1.76 (m, 1H, CH), 1.68 - 1.65 (m, 2H, CH_2), 0.96 (d, $^3J_{H-H} = 6.5$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8 (CO), 145.8, 140.6, 135.9 (C_q), 129.5, 128.6, 128.4, 127.7, 127.5 (CH), 39.8, 32.2, (CH_2), 37.6 (CH), 15.2 (CH_3).

X-ray Diffraction Studies. Single crystals of **1**, **3**, and **4** were mounted on a glass fiber in a random orientation. Data collection was performed at room temperature on a Siemens Smart CCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) with a nominal crystal to detector distance of 4.0 cm. Space group assignment was based on systematic absences, E statistics, and successful refinement of the structures. The structure was solved by direct methods with the aid of successive difference Fourier maps and were refined using the SHELXTL 6.1 software package.[27] All non-hydrogen were refined anisotropically. Hydrogen atoms were assigned to ideal positions and refined using a riding model. Details of the data collection, cell dimensions, and structure refinement are given in Table 3. The diffraction frames were integrated using the SAINT package.[28]

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Supporting Information Available: Full crystallographic data is available as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JA906028G

(27) Sheldrick, G. M. *SHELXTL, version 6.1*; Bruker AXS, Inc.: Madison, WI, 2000.
(28) *SAINT, Bruker Analytical X-ray System, version 5.0*; Bruker AXS, Inc.: Madison, WI, 1998.