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Note

N-Heterocyclic carbene adducts of cyclopalladated ferrocenylpyridine: Synthesis, structural characterization and reusable catalytic system for Suzuki and amination of aryl chlorides in poly(ethylene glycol-400)

Chen Xu [a,*], Hong-Mei Li [b], Hu Liu [b], Zhi-Qiang Zhang [b], Zhi-Qiang Wang [a], Wei-Jun Fu [a], Yu-Qing Zhang [b,*]

[a] College of Chemistry and Chemical Engineering, Luoyang Normal University, Luoyang, Henan 471022, China
[b] Henan University of Science and Technology, School of Chemical Engineering and Pharmaceutics, Luoyang, Henan 471003, China

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ABSTRACT

Two air-stable carbene adducts of cyclopalladated ferrocenylpyridine **1**–**2** have been synthesized and characterized by elemental analysis, IR, ESI-MS, ^{1}H and 13C NMR. Additionally, their detailed structures have been determined by single-crystal X-ray analysis. The use of these complexes as catalysts for the Suzuki and Buchwald–Hartwig amination of aryl chlorides was examined. Compound **2** was found to be very efficient for these reactions. Typically, using 0.5–1 mol% of catalyst in the presence of 3 equivalents of K^{t}OBu as base in PEG-400 [poly(ethylene glycol-400)] at 120 °C provided coupling products in excellent yields. Moreover, the **2**/PEG-400 system could be recycled and reused three times.

1. Introduction

Palladium-catalyzed coupling reactions such as the Suzuki coupling and the Buchwald–Hartwig amination have become an extremely powerful method in organic synthesis for the formation of carbon–carbon or carbon–heteroatom bonds [1]. Employing aryl chlorides for this reaction has been a focus because aryl chlorides are cheaper and more available than their bromides and iodide counterparts [2]. In recent years, *N*-heterocyclic carbenes (NHCs) have become a paradigmatically new generation of strong σ-donor ligands and widely used in palladium-catalyzed coupling reactions [3–5]. Among them, a combination of a palladacycle framework with highly donating and sterically demanding NHCs has been reported [6–11]. However, in most cases the catalysts employed need to be used in relatively high loadings (1–2 mol%) [6–9], and poor recovery, which negated the advantages associated with the use of aryl chlorides. PEGs have clear advantages as a solvent in organic synthesis because they are cheap, steady, readily available, and nontoxic [12,13]. Recently, liquid PEGs have been adopted as a new approach for catalyst recycling, in a broad range of catalytic organic reactions [14–16].

We have also found biaryl phosphine adducts of cyclopalladated ferrocenylpyrimidine are very efficient for the amination of aryl chlorides in PEG-400 [17]. The above adducts combine the stability induced by the presence of a palladacycle framework with the high activity commonly associated with phosphine ligands, and were far more active than the corresponding dimeric palladacycle. Moreover, the palladacycles containing halide acted as substrates and efficient catalysts in the coupling reactions [18]. In view of these findings and our continuous interest in the synthesis and application of cyclopalladated complexes [17–20], we prepared two carbene adducts of palladacycle **1**–**2** (Scheme 1) and examined their catalytic activity in Suzuki and Buchwald–Hartwig amination. Here, we report that **2**, in combination with PEG-400 as the solvent, is an extremely effective and reusable system for the coupling reactions of aryl chlorides.

2. Experimental

2.1. General procedures

Solvents were dried and freshly distilled prior to use. All other chemicals were commercially available expect for the chloride-bridged palladacyclic dimer A which was prepared according to the published procedure [18]. Elemental analyses were determined with a Carlo Erba 1160 Elemental Analyzer. IR spectra were collected on a Bruker VECTOR22 spectrophotometer in KBr pellets. NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were measured on a LC-MSD-Trap-XCT instrument. Crystallographic data were collected on a Bruker SMART APEX-II CCD diffractometer.

* Corresponding authors.
E-mail addresses: xubohan@163.com (C. Xu), zhangyq8@126.com (Y.-Q. Zhang).

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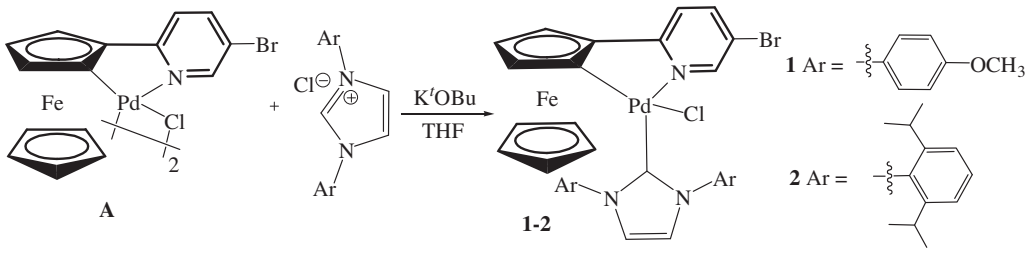


Scheme 1. Synthesis of **1**–**2**.

2.2. General procedure for the synthesis of carbene adducts of cyclopalladated ferrocenylpyridine ***1***–***2***

A Schlenk tube was charged with the palladacyclic dimer **A** (0.1 mmol), 1,3-di-4-methoxyphenylimidazolium chloride or 1, 3-bis(2,6-diisopropylphenyl) imidazolium chloride (IPrHCl) (0.25 mmol) and K^{t}OBu (0.3 mmol) under nitrogen. Dry THF was added by a cannula and stirred at room temperature for 3 h. The product was separated by passing through a short silica gel column with CH_2Cl_2 as eluent, the second band was collected and afforded the corresponding carbene adduct of cyclopalladated ferrocenylpyridine complex **1**–**2**.

2.2.1. [PdCl{[(η^5-C_5H_5)]Fe[(η^5-C_5H_3)–NC_5H_3–Br]}($C_3N_2H_2$)(C_6H_4–OCH_3)$_2$] (***1***)

Red solid, yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H, py), 8.35 (d, J = 8.8 Hz, 2H, Ar), 7.80 (d, J = 8.8 Hz, 2H, Ar), 7.58 (d, J = 8.4 Hz, 1H, py), 7.40 (s, 1H, NCHCHN), 7.33 (s, 1H, NCHCHN), 7.12 (d, J = 8.8 Hz, 2H, Ar), 6.89 (d, J = 8.4 Hz, 1H, py), 6.82 (d, J = 8.8 Hz, 2H, Ar), 4.35 (s, 1H, C_5H_3), 4.11 (s, 1H, C_5H_3), 3.79 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.44 (s, 5H, C_5H_5), 3.32 (s, 1H, C_5H_3). ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 164.9, 150.9, 146.5, 140.4, 137.8, 136.7, 135.2, 134.5, 133.7, 132.1, 127.2, 126.5, 123.3, 122.8, 118.1, 116.3, 114.8, 114.4, 114.2, 94.4, 87.2, 73.3, 70.1, 68.7, 63.0, 55.8, 55.6. MS-ESI$^+$: m/z 726.0 [M$^+$–Cl]. IR (KBr, cm^{-1}): 2934, 1598, 1510, 1492, 1451, 1410, 1371, 1305, 1249, 1175, 1106, 941, 838, 814, 737, 692, 662. *Anal.* Calc. for $C_{32}H_{27}BrClFeN_3O_2Pd$: C, 50.36; H, 3.57; N, 5.51. Found: C, 50.57; H, 3.38; N 5.75%.

2.2.2. [PdCl{[(η^5-C_5H_5)]Fe[(η^5-C_5H_3)–NC_5H_3–Br]}($C_3N_2H_2$)(C_6H_3–$2C_3H_7$)$_2$] (***2***)

Red solid, yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H, py), 7.56 (d, J = 8.4 Hz, 1H, py), 7.45–7.49 (m, 3H, NCHCHN + Ar), 7.29–7.38 (m, 2H, Ar), 7.17–7.21 (m, 2H, Ar), 7.06 (d, J = 7.6 Hz, 1H, Ar), 6.91 (d, J = 8.4 Hz, 1H, py), 4.63–4.66 (m, 1H, CH), 4.44 (s, 1H, C_5H_3), 4.22 (s, 1H, C_5H_3), 3.81 (s, 1H, C_5H_3), 3.35 (s, 5H, C_5H_5), 3.16–3.19 (m, 1H, CH), 2.87–2.96 (m, 2H, CH), 1.58–1.62 (m, 6H, CH_3), 1.55 (d, J = 6.4 Hz, 3H, CH_3), 1.42 (d, J = 6.0 Hz, 3H, CH_3), 1.19 (d, J = 6.4 Hz, 3H, CH_3), 0.98 (d, J = 6.4 Hz, 3H, CH_3), 0.85 (d, J = 6.4 Hz, 3H, CH_3), 0.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 164.7, 151.2, 148.1, 147.1, 145.5, 144.6, 140.1, 136.7, 136.4, 130.3, 130.0, 125.4, 125.0, 124.9, 124.6, 124.4, 123.4, 117.4, 113.8, 95.7, 86.9, 72.3, 70.5, 68.8, 62.9, 29.1, 29.0, 28.6, 28.5, 27.9, 27.3, 25.5, 25.1, 23.8, 23.5, 23.4, 21.7. MS-ESI$^+$: m/z 834.1 [M$^+$–Cl]. IR (KBr, cm^{-1}): 2960, 1593, 1492, 1459, 1443, 1406, 1331, 1306, 1277, 1265, 1105, 1027, 931, 909, 828, 816, 796, 762, 752, 739, 704. *Anal.* Calc. for $C_{42}H_{47}BrClFeN_3Pd$: C, 57.89; H, 5.44; N, 4.82. Found: C, 58.05; H, 5.31; N 4.97%.

2.3. General procedure for the Suzuki and amination of aryl chlorides

In a Schlenk tube, a mixture of the prescribed amount of catalyst, aryl chloride (1.0 mmol), phenyl boronic acid (1.5 mmol) or amine (1.5 mmol) and the selected base (3.0 mmol) in PEG-400 (3 mL) was evacuated and charged with nitrogen. The reaction mixture was then placed in an oil bath and heated at 120 °C for 16–24 h. After being cooled, the mixture was extracted with dry diethyl ether and evaporated, the residue was isolated by flash chromatography on silica gel to afford the desired coupled products. After extracting with diethyl ether, the mixture of catalyst, and PEG-400 was solidified (cooled and then evaporated under vacuo) and subjected to a second run of the amination by charging with the same substrates.

3. Results and discussion

3.1. Synthesis and characterization of complexes ***1***–***2***

Two new carbene adducts of palladacycle **1**–**2** have been easily prepared *in situ* from the reaction of the chloride-bridged palladacyclic dimer and the corresponding imidazolium salt in THF at room temperature under N_2 (Scheme 1). The one-pot synthesis avoids multi-step reactions employing free carbenes [21]. These new complexes were fully characterized by elemental analysis, IR, ESI-MS, NMR. The ^{1}H NMR spectra of these complexes were consistent with the proposed structures and showed only one set of signals in a symmetrical surrounding indicating the exclusive formation of one isomer.

The crystals were obtained by recrystallization from CH_2Cl_2–petroleum ether solution at room temperature. The molecules are shown in Fig. 1 and 2. The Pd atom in each complex is in a

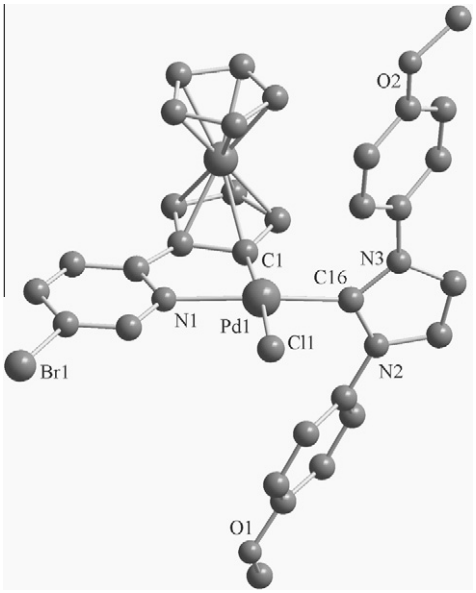


Fig. 1. Molecular structure of complex **1**·CH_2Cl_2. CH_2Cl_2 and H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(1) 1.973(3), Pd(1)–C(16) 1.977(3), Pd(1)–N(1) 2.108(3), Pd(1)–Cl(1) 2.4391(9), and C(1)–Pd(1)–Cl(1) 173.48(9), C(16)–Pd(1)–N(1) 168.58(11), C(16)–Pd(1)–C(1) 90.34(13), C(1)–Pd(1)–N(1) 80.90(12).

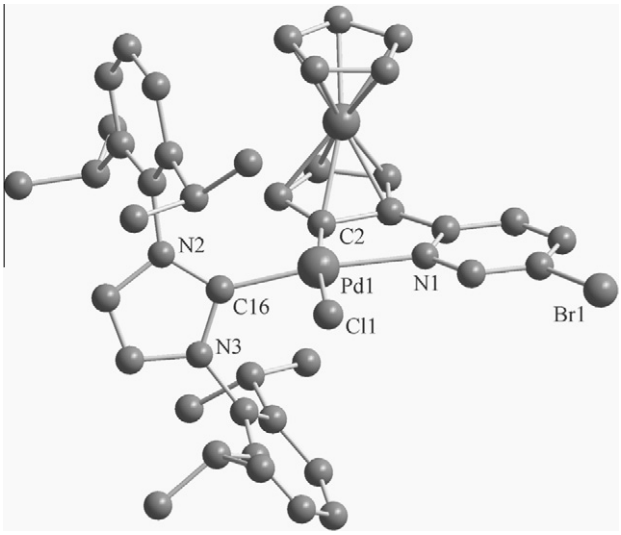


Fig. 2. Molecular structure of complex **2**. H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(2) 1.973(3), Pd(1)–C(16) 1.995(3), Pd(1)–N(1) 2.122(2), Pd(1)–Cl(1) 2.3888(10), and C(2)–Pd(1)–Cl(1) 173.06(8), C(16)–Pd(1)–N(1) 170.61(11), C(16)–Pd(1)–C(2) 95.77(11), C(2)–Pd(1)–N(1) 80.87(11).

slightly distorted square-planar environment bonded to the C atom of NHC, the chlorine atom, the nitrogen atom and the C atom of the ferrocenyl moiety. The Pd–C_{carb} [1.995(3) Å] bond length of complex **2** is similar to those of related carbene adducts [1.992–1.998 Å] [10,22], while it is longer than those of related complexes **1**·CH_2Cl_2 [1.977(3) Å] possibly due to the steric bulk of the IPr ligand. The imidazole ring plane of NHC is almost perpendicular to the square plane formed by the Pd(II) center (dihedral angles of 95.3°, 74.4° for complexes **1**·CH_2Cl_2, **2**, respectively). In this type of arrangement the N-substituents of NHC reduce the steric interaction with palladacyclic ligand.

3.2. The Suzuki coupling

In 2005, Li. et al. developed a highly efficient and reusable $Pd(OAc)_2$/DABCO (triethylene-diamine)/PEG system for the Suzuki coupling [23]. However, the catalytic system could not be reused for the reaction of aryl chlorides. To the best of our knowledge, there was no report concerning the reusable catalytic system for the Suzuki coupling of aryl chlorides in PEGs. Our initial exploration of reaction conditions focused on the coupling of chlorobenzene with phenylboronic acid using 0.5 mol% of **2** in PEG-400 at 120 °C for 16 h. After screening a variety of bases (Table 1, entries 1–6), K^{t}OBu was found to give the best result. Other conditions (0.1 mol% of **2** or 80 °C) afforded low coupled product yields (33% and 47%, respectively. data not shown). However, **1** was almost inactive under the same reaction conditions (entry 7) and the yield was improved by the addition of IPrHCl (40%, entry 8) suggesting that carbene ligand IPr participated in the catalytic cycles. It was shown that the cyclopalladated ligand was released from the metal center during activation of the Pd(II) precatalyst. We proposed that the coupling reaction catalyzed by palladacycle proceeded through a Pd(0)/Pd(II) cycle [18,24,25].

To check the reusability of the solvent PEG-400 as well as the catalyst, the same reaction was first examined in the presence of 0.5 mol% of **2**. After initial experimentation, the reaction mixture was extracted with dry diethyl ether, and the PEG and catalyst were solidified and subjected to a second run of the Suzuki coupling by charging with the same substrates. The results of this experiment and two subsequent experiments were consistent in yields (98%, 96% and 93%, respectively, entry 9). In the following

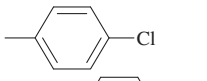
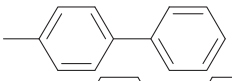
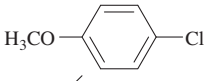
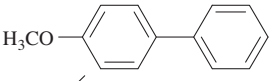
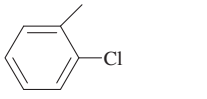
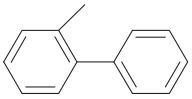
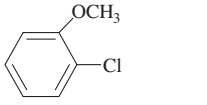
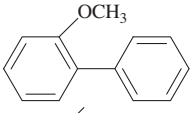
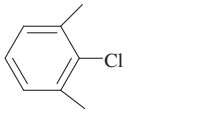
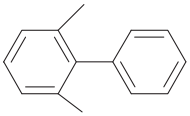
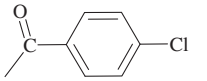
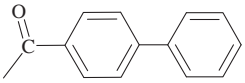
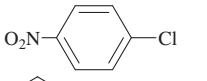
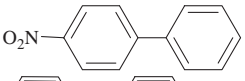
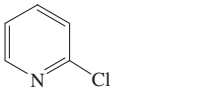
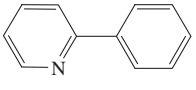
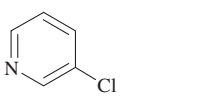
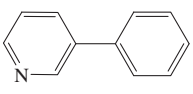
Table 1
Influence of base and catalyst on the Suzuki coupling of phenyl chloride with phenyl boronic acid.[a]

Entry	Catalyst (mol%)	Base	Yield(%)[b]
1	**2**(0.5)	Cs_2CO_3	43
2	**2**(0.5)	K_2CO_3	48
3	**2**(0.5)	Na_2CO_3	31
4	**2**(0.5)	KOH	39
5	**2**(0.5)	Na^{t}OBu	72
6	**2**(0.5)	K^{t}OBu	98
7	**1**(0.5)	K^{t}OBu	trace
8	**A**/IPrHCl (0.25/1)	K^{t}OBu	40
9	Entry 6 cycle 1, 2, 3	K^{t}OBu	98, 96, 93

[a] Reaction conditions: PhCl (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), base (3.0 mmol), PEG-400 (3 mL), 120 °C, 16 h.
[b] Isolated yields (average of two experiments).

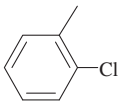
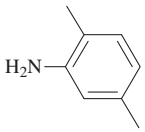
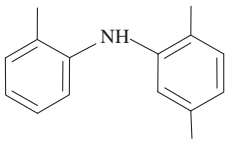
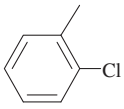
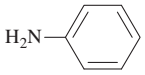
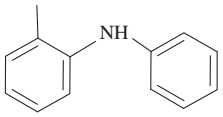
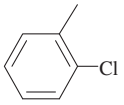
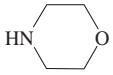
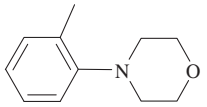
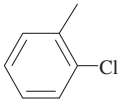
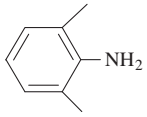
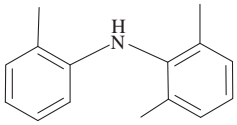
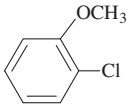
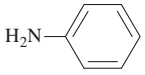
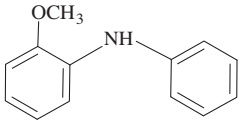
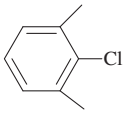
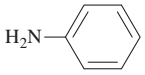
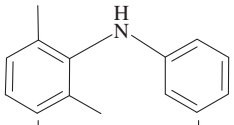
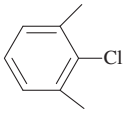
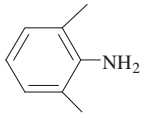
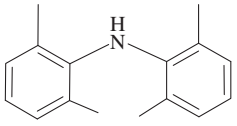
experiments, the Suzuki coupling of a variety of electronically and structurally diverse aryl chlorides with phenylboronic acid was investigated under the same reaction conditions (Table 2). Similar to the result of chlorobenzene, excellent yields (95–96%) were also obtained in the case of other electron-rich aryl chlorides (entries 1–2). *Ortho*-substituents were tolerated and even the very sterically hindered 2-chloro-m-xylene provided the product in 88% isolated yield (entries 3–5). For electron-deficient aryl chlorides, they could be coupled very efficiently with a catalytic loading as low as 0.1 mol% (entries 6–7). Finally, heteroaryl chlorides such as 2-chloropyridine and 3-chloropyridine were found to be efficient coupling partners in this system (entries 8–9).

Table 2
Suzuki coupling of aryl chlorides with phenyl boronic acid catalyzed by **2**.[a]

Entry	Aryl halide	Product	Yield(%)[b]
1			96
2			95
3			93
4			92
5			88
6[c]			97
7[c]			98
8			96
9			90

[a] Reaction conditions: catalyst **2** (0.5 mol%), aryl chloride (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), K^{t}OBu (3.0 mmol), PEG-400 (3 mL), 120 °C, 16 h.
[b] Isolated yields (average of two experiments).
[c] Catalyst **2** (0.1 mol%).

Table 3
Aminations of various amines with hindered aryl chlorides catalyzed by **2**.[a].

Entry	Aryl Chloride	Amine	Product	Yield(%)[b]
1				92
2	Entry 1 cycle 1, 2, 3			91, 88, 83
3				95
4				90
5				89
6				93
7				87
8				84

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.5 mmol), K^{t}OBu (3.0 mmol), **2** (1 mol%), PEG-400 (3 mL), 120 °C, 24 h.
[b] Isolated yields (average of two experiments).

3.3. The Buchwald–Hartwig amination

The high activity of **2** in the Suzuki coupling of aryl chlorides encouraged us to examine its activity toward the Buchwald–Hartwig amination. Based on our previous experiments [17], the reaction of 2-chlorotoluene with 2,5-dimethylaniline was performed under nitrogen atmosphere in PEG-400 in the presence of 1 mol% of **2** as catalyst and K^{t}OBu as base at 120 °C for 24 h, affording the coupled product in 92% yield (Table 3, entry 1). We also observed that the above catalytic system could be recycled and reused three times without loss of activity for the same reaction (entry 2). Furthermore, a variety of electronically and structurally diverse aryl chlorides could be coupled efficiently with various amines under the same conditions. Similar to the result of the 2,5-dimethylaniline, the reactions of aniline, morpholine and 2, 6-dimethylbenzenamine with 2-chlorotoluene provided high isolated yields (89–95%, entries 3–5). For the very sterically hindered 2-chloro-*m*-xylene also gave the desired products in high yields (entries 7–8).

4. Conclusions

Two carbene adducts of cyclopalladated ferrocenylpyridine **1**–**2** have been easily synthesized. Their catalytic activity was evaluated in the Suzuki and Buchwald–Hartwig amination of aryl chlorides. **2** was found to be very efficient for these reactions. Currently, further efforts to extend the applications involving this type of palladacycle in other palladium-catalyzed reactions are underway in our laboratory.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2012.01.063.

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