

# Cyclic Carbonates as Green Alternative Solvents for the Heck Reaction

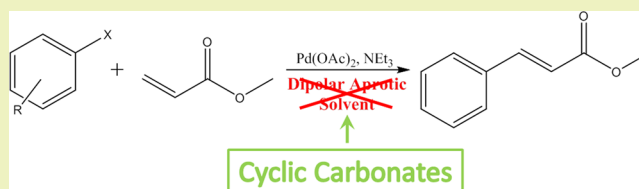
Helen L. Parker, James Sherwood, Andrew J. Hunt,\* and James H. Clark

Green Chemistry Centre of Excellence, University of York, York, United Kingdom, YO10 5DD

## Supporting Information

**ABSTRACT:** Organic cyclic carbonates (ethylene and propylene carbonate) are shown to be viable greener solvents for use in Heck reactions, offering a highly effective alternative to traditionally used dipolar aprotic solvents such as NMP, DMF, and DMAc.

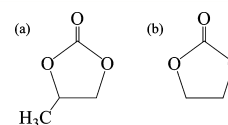
**KEYWORDS:** Green solvents, Kamlet–Taft, REACH, Palladium, Dipolar aprotic solvents



## INTRODUCTION

The importance of utilizing greener solvents has permeated into all aspects of synthetic chemistry, and palladium-catalyzed Heck reactions are no different.<sup>1,2</sup> Heck reactions are ubiquitous in the pharmaceutical industry in both medicinal chemistry and drug manufacture.<sup>3</sup> Traditionally, cross-coupling reactions are preferentially carried out in highly dipolar aprotic solvents, e.g., *N,N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), and *N,N*-dimethylacetamide (DMAc).<sup>4</sup> Although these solvents offer high performance in Heck reactions, this is only one of a number of considerations that should be prioritized by the contemporary chemist. In a typical reaction, the majority of the material input (and subsequently much of the associated waste) is a combination of the reaction solvent and any additional solvents used for the purification of the product.<sup>5</sup> The impact of solvents on the environment, in terms of both pollution and depletion of resources must therefore be considered. The amide solvents, NMP and DMF especially, present appreciable hazards to human health.<sup>6</sup> It is also likely that under REACH (Regulation, Evaluation, Authorization and restriction of CHEmicals),<sup>7</sup> and other chemical-related legislation some, if not all, of these solvents will be subject to authorization or restrictions in the future. The related Suzuki cross-coupling reaction is very amenable to alcohol solvents, which are generally regarded as green reaction media.<sup>8–10</sup> However, our trial reactions with alcohol solvents showed that the Heck reaction proceeds slowly, if at all, in protic solvents. As we seek alternative solvents, we should be aware of incentives to encourage the use of biobased chemicals. The EU is prioritizing the uptake of the major classes of renewable chemicals, including solvents, as reflected in the production of new standards and certification schemes.<sup>11</sup> Accordingly, the substitution of existing dipolar aprotics in favor of more benign alternatives, such as cyclic carbonates, is greatly beneficial (Figure 1).

In order to justify a replacement solvent, reaction efficiency must not be compromised to simply reduce the environmental



**Figure 1.** Structures of (a) propylene carbonate and (b) ethylene carbonate.

burden. Inferior reaction performance is not appealing on the grounds of increased waste and energy consumption, not to mention any economic implications. Previous work investigating greener solvents for Heck reactions has included the use of water and supercritical CO<sub>2</sub>; however, such systems are not ideal as they often show reduced activity requiring longer reaction times. This also leads to significantly more catalyst or a modified catalyst being used.<sup>12–15</sup> The search for greener solvent replacements can be systemized and provide additional justifications for any proposed substitution.<sup>16,17</sup> Identification of solvent properties that promote the efficiency of Heck reactions is essential as it will enable informed choices for alternative solvents to be made. Until now, a detailed study correlating solvent properties with performance for the Heck reaction did not exist. In this paper, a systematic approach has been applied to the optimization of solvents properties for Heck reactions, including both reaction efficiency and green credentials of the solvents. This work has highlighted two greener alternatives to traditional dipolar aprotic solvents in Heck coupling reactions.

## MATERIALS AND METHODS

**Rate of Reaction Screening Tests.** Into a 250 mL round-bottomed flask, the following reagents were measured: iodobenzene (30 mmol), methyl acrylate (30 mmol), and triethylamine (30 mmol). Solvent 30 mL was then added, and the flask heated with stirring to 373 K. An excess of solvent was used in these reactions in order for the

**Received:** April 28, 2014

**Revised:** May 23, 2014

**Published:** May 27, 2014

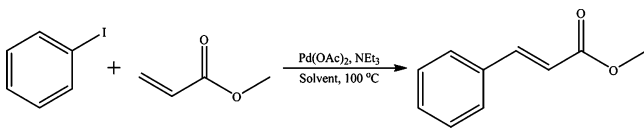
reaction to proceed at a speed that could be accurately monitored. Once the flask had been heated to the required temperature, Pd(OAc)<sub>2</sub> (0.1 mol %) catalyst was added. For control experiments, no catalyst was added. The reaction was monitored with samples taken at designated intervals. The reaction was allowed to proceed until the yield had reached >50%. The reaction was monitored by GC-FID using diethyl succinate as a standard.

**Reactions with Other Aryl Halides.** Into a 25 mL round-bottomed flask, the following reagents were measured: aryl halide (15 mmol), methyl acrylate (1.2 mol eqv), and triethylamine (1.2 mol eqv). A total of 6 mL of solvent was then added, and the flask heated with stirring to 373 K. Once the flask had been heated to the required temperature, Pd(OAc)<sub>2</sub> (0.3 mol %) catalyst was added. For control experiments, no catalyst was added. Reaction conversions were determined by <sup>1</sup>H NMR spectroscopy. For purification, after completion, the reaction product was extracted from the solvent using 3 mL × 5 mL ethyl acetate. The organic fractions were combined and the solvent removed *in vacuo*. Purification was carried out by silica gel column chromatography using hexane:ethyl acetate (99:1). Characterization by NMR and mass spectrometry was consistent with existing literature examples.

## RESULTS AND DISCUSSION

First, a screening of the reaction rates of a model Heck reaction at 100 °C was undertaken with the following conventional dipolar or polarizable solvents and neoteric solvents: cyclohexanone, *p*-cymene, DMF, dimethyl sulfoxide (DMSO), ethylene carbonate, NMP, propylene carbonate, and toluene (Scheme 1). As shown from their entries in the GlaxoSmithK-

**Scheme 1. Model Heck Reaction Used To Determine Rates of Reaction in Different Solvents**



**Table 1. Greenness of Solvents Used in the Heck Reaction<sup>21</sup>**

solvent <sup>a</sup>	waste <sup>b</sup>	E-impact <sup>b</sup>	health <sup>b</sup>	flammability <sup>b</sup>	reactivity <sup>b</sup>
cyclohexanone	6	8	6	8	9
DMF	4	6	2	9	9
DMSO	5	5	7	9	2
ethylene carbonate	6	7	5	10	9
NMP	5	6	3	9	8
propylene carbonate	6	7	5	8	9
toluene	6	3	4	4	10

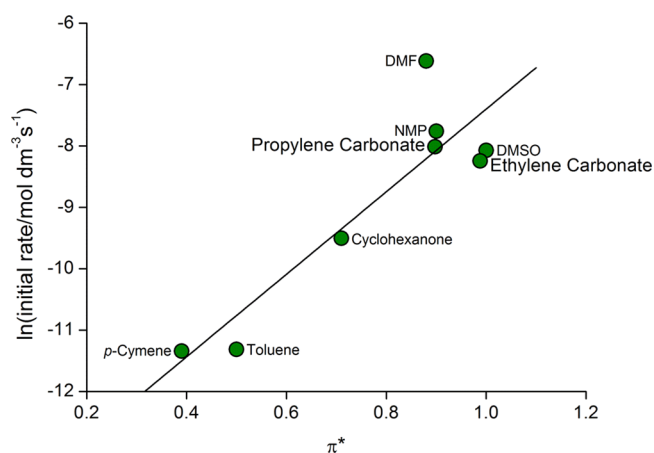
<sup>a</sup>No data was available for *p*-cymene. <sup>b</sup>Full explanation of the terms used can be found in the Supporting Information.

line (GSK) solvent selection guide (Table 1), toluene and the dipolar aprotic solvents each have one area of concern (each highlighted in red) regarding either their safety during use or their environmental impact after use.<sup>18</sup> Cyclohexanone, ethylene carbonate, and propylene carbonate show no areas of concern, maintaining good to excellent ratings across all of the criteria. Cyclic ketone and carbonate solvents have been demonstrated to be satisfactory solvents in applications usually dependent on more toxic dipolar aprotics, which suggested they may be applicable to Heck reactions.<sup>19,20</sup> There was no data

available for *p*-cymene, but as a successful biobased replacement for toluene its selection was justified.<sup>16</sup>

Organic carbonates, particularly cyclic carbonates, have significant benefits as eco-friendly solvents due to their biodegradability, low vapor pressure, odor levels, and toxicities.<sup>2,22</sup> Carbonates are also dipolar aprotic solvents and available on an industrial scale at relatively low costs.<sup>23,24</sup> Furthermore, the synthesis of organic carbonates is also becoming greener.<sup>25–27</sup> Eghbali et al. have developed a highly efficient method to convert alkenes (including bioethene from ethanol) and CO<sub>2</sub> directly into cyclic carbonates.<sup>28</sup> This sustainable synthesis of carbonates using renewable feedstocks increases the environmental benefits and long-term potential of using these solvents.

From the results of solvent screening, the initial rate of reaction to give methyl cinnamate was plotted against the different Kamlet–Taft solvent parameters (Table SI-1, Supporting Information). It was found that the initial rate was proportional to the dipolarity of the solvent, as gauged with the Kamlet–Taft solvatochromic  $\pi^*$  scale (Figure 2 and Table



**Figure 2. Relationship between solvent dipolarity and the natural logarithm of the initial reaction rate.**

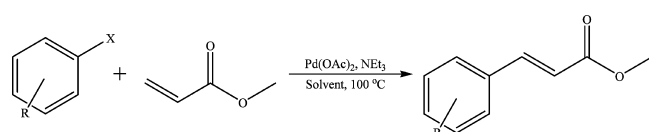
SI-1, Supporting Information).<sup>29,30</sup> The complementary parameter describing hydrogen bond-accepting ability ( $\beta$ ) was found to be statistically insignificant. No protic solvents were suitable for this study to evaluate the role of hydrogen bond donating ability ( $\alpha$ ), although trial reactions in refluxing *t*-butanol were incredibly slow (i.e., 6% conversion, in 45 h). The linear relationship based on  $\pi^*$  is statistically sound (*p*-value of 0.0025) except for DMF, which is a significant outlier. There is no obvious reason why this should be so, but ultimately, considering its reproductive toxicity, the rate enhancement achieved with DMF is not substantial enough to justify its use.

The observed solvent effect is consistent with the common proposal that alkene insertion by palladium is the rate-determining step of the Heck reaction with aryl iodides.<sup>31–34</sup> The polarization of the alkene results in a separation of charge that is presumably best stabilized in highly dipolar solvents, thus the reaction is accelerated by solvents like DMF. The dependence of the reaction rate on the dipolarity of the solvent meant that neither toluene nor *p*-cymene were suitable solvents for this Heck reaction. Cyclohexanone is more dipolar than an aromatic solvent but still cannot compete with NMP, DMF, or similar solvents. However, ethylene carbonate ( $\pi^* = 0.99$ ) and propylene carbonate ( $\pi^* = 0.90$ ) did promote high

productivity. Both ethylene and propylene carbonate have higher boiling points (and lower vapor pressures) compared to NMP or DMF, which lowers atmospheric emissions, and are certainly safer to handle and less toxic in most respects. Also consisting entirely of carbon, hydrogen, and oxygen, after use the cyclic carbonates create no NO<sub>x</sub> or SO<sub>x</sub> air pollution upon incineration. The primary disadvantage of ethylene carbonate is that it is a solid at room temperature, but propylene carbonate has a similar melting point to DMF. Overall ethylene carbonate and propylene carbonate are appealing solvents, especially as replacements for NMP and DMF in Heck coupling reactions.

To further explore the scope and possible limitations of ethylene and propylene carbonate as green alternative solvents, additional Heck reactions were carried out using a range of different substituted aryl halides (Table 2). All reactions were

**Table 2. Comparison of Reaction Efficiency for a Range of Substituted Aryl Halides Using Cyclic Carbonates and NMP as Solvents**



entry	X	R'	% conversion <sup>a,b</sup>		
			NMP	propylene carbonate	ethylene carbonate
1	I	H	96	100	99
2	I	4-Cl	96	97	100
3	I	3-NO <sub>2</sub>	91	93	90
4	I	4-COCH <sub>3</sub>	93	92	96
5	Br	H	0	0	40
6	Br	2-NO <sub>2</sub>	99	97	100
7	Br	4-COCH <sub>3</sub>	95	85	100
8	Br	2-COCH <sub>3</sub>	100	100	100
9	Br	4-CN	100	100	100

<sup>a</sup>Conversion calculated from <sup>1</sup>H NMR spectra. <sup>b</sup>Reaction conditions: aryl halide (15 mmol), methyl acrylate (1.2 mol eqv), triethylamine (1.2 mol eqv), Pd(OAc)<sub>2</sub> (0.3 mol %) solvent (6 mL), 100 °C, and 24 h (reaction time not optimized).

carried out at 100 °C with 0.3 mol % of Pd(OAc)<sub>2</sub>. The solvent NMP was tested alongside the carbonate solvents to give a benchmark for yields achieved using conventional Heck solvents.

Various substituent groups on iodobenzene were tested in order to determine any changes that could arise due to the use of different solvents (Table 2, entries 1–4). Results indicated that comparable or superior conversions were achieved when using carbonate solvents against NMP. The same procedure of separation and purification of product was also successfully applied to each solvent (NMR of purified products, Figure SI-2, Supporting Information). Encouragingly, when using ethylene carbonate, the majority of conversions were higher than those achieved for NMP. Reactions were also conducted using less reactive substituted aryl bromide reagents (Table 2, entries 5–9).<sup>35</sup> The performance of propylene carbonate was comparable to NMP under the conditions tested. In many cases, ethylene carbonate outperformed NMP and resulted in 100% conversions in the majority of aryl bromides tested (entries 6–8). Most noteworthy was the cross-coupling of bromobenzene in ethylene carbonate, which gave a 40% conversion to the

product. This was in significant contrast to both NMP and propylene carbonate, which gave no conversion (entry 5). This is a difficult reaction to initiate, and the success of ethylene carbonate as a solvent establishes it as a suitable replacement solvent for these types of reactions.

## CONCLUSION

This work has illustrated that it is the solvent polarity that is the driving force for effective Heck catalysis, and it is this property that should be considered when developing greener reaction methods in the future. The solvent studies presented have also highlighted that cyclic carbonates have great potential for use as greener solvents in Heck reactions; encouragingly, in many cases, these solvents may outperform traditional dipolar aprotic solvents such as NMP. Further work will include more testing of different substrates in the Heck reaction, including substrates with electron-donating groups and also the development of purification procedures suited specifically to the cyclic carbonate solvents.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedure: Rate of reaction screening tests, reactions with other aryl halides. Characterization of Pd(OAc)<sub>2</sub>. Explanation of terms used in Table 1. Calculation of Kamlet–Taft parameters. Kamlet–Taft parameters of solvents used for Heck reactions. Mechanism of Heck reaction stabilized by highly dipolar solvents. <sup>1</sup>H NMR of purified E-methyl-4-chlorocinnamate from reactions using solvents NMP, EC, and PC. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [andrew.hunt@york.ac.uk](mailto:andrew.hunt@york.ac.uk). Fax: (+) 44 (0) 1904 332705. Tel: (+) 44 (0) 1904 322546.

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## REFERENCES

- (1) Liu, S.; Xiao, J. Toward green catalytic synthesis – Transition metal-catalyzed reactions in non-conventional media. *J. Mol. Catal. A: Chem.* **2007**, *270* (1–2), 1–43.
- (2) Kerton, F. M.; Marriott, R. *Alternative Solvents for Green Chemistry*; Royal Society of Chemistry: London, 2013; Vol. 20.
- (3) Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. Nickel-catalyzed suzuki-miyaura couplings in green solvents. *Org. Lett.* **2013**, *15*, 3950–3953.
- (4) Beletskaya, I. P.; Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.
- (5) Jiménez-González, C.; Curzons, A. D.; Constable, D. J.; Cunningham, V. L. Cradle-to-gate life cycle inventory and assessment of pharmaceutical compounds. *Int. J. Life Cycle Assess.* **2004**, *9* (2), 114–121.
- (6) Candidate List of Substances of Very High Concern for Authorisation. European Chemicals Agency. <http://echa.europa.eu/candidate-list-table> (accessed September 12, 2013).

- (7) Registration, Evaluation, Authorisation and restriction of CHemicals (REACH). <http://www.hse.gov.uk/reach/> (accessed March 12, 2013).
- (8) Lygo, B.; Andrews, B. I. Enantioselective synthesis of aroylalanine derivatives. *Tetrahedron Lett.* **2003**, *44*, 4499–4502.
- (9) Lu, B. Z.; Li, G.; Rodriguez, S.; Liu, J.; Eriksson, M. C.; Tan, Z.; Song, J. J.; Yee, N. K.; Farina, V.; Senanayake, C. H. Development of a practical synthesis of 4-[6-(morpholinomethyl)-pyridin-3-yl]-naphthalen-1-amine, a key intermediate for the synthesis of BIRB 1017, a potent p38 MAP kinase inhibitor. *Synlett* **2013**, *24*, 0317–0322.
- (10) Camp, J. E.; Dunsford, J. J.; Cannons, E. P.; Restorick, W. J.; Gadzhieva, A.; Fay, M. W.; Smith, R. J. Glucose-derived palladium(0) nanoparticles as in situ-formed catalysts for Suzuki–Miyaura cross-coupling reactions in isopropanol. *ACS Sustainable Chem. Eng.* **2014**, *2*, 500–505.
- (11) European Committee for Standardisation. <http://www.cen.eu/cen/Sectors/Sectors/Biobased/Pages/default.aspx> (accessed October 12, 2013).
- (12) Cacchi, S.; Fabrizi, G.; Gasparrini, F.; Villani, C. Carbon–carbon bond forming reactions in supercritical carbon dioxide in the presence of a supported palladium catalyst. *Synlett* **1999**, *3*, 345–347.
- (13) Anson, M. S.; Mirza, A. R.; Tonks, L.; Williams, J. M. J. Palladium catalyzed Heck and enantioselective allylic substitution reactions using reverse phase silica supports. *Tetrahedron Lett.* **1999**, *40* (39), 7147–7150.
- (14) Alacid, E.; Najera, C. Palladated kaiser oxime resin as precatalyst for the Heck reaction in organic and aqueous media. *Synlett* **2006**, *18*, 2959–2964.
- (15) Martinez, S.; Vallribera, A.; Cotet, C. L.; Popvici, M.; Martin, L.; Roig, A.; Moreno-Manas, M.; Molins, E. Nanosized metallic particles embedded in silica and carbon aerogels as catalysts in the Mizoroki–Heck coupling reaction. *New J. Chem.* **2005**, *29*, 1342–1345.
- (16) Clark, J. H.; Macquarrie, D. J.; Sherwood, J. The combined role of catalysis and solvent effects on the Biginelli reaction: improving efficiency and sustainability. *Chem.—Eur. J.* **2013**, *19* (16), 5174–82.
- (17) Clark, J. H.; Macquarrie, D. J.; Sherwood, J. A quantitative comparison between conventional and bio-derived solvents from citrus waste in esterification and amidation kinetic studies. *Green Chem.* **2012**, *14* (1), 90.
- (18) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK's solvent selection guide – Embedding sustainability into solvent selection starting at medicinal chemistry. *Green Chem.* **2011**, *13* (4), 854.
- (19) Reetz, M. T.; Lohmer, G. Propylene carbonate stabilized nanostructured palladium clusters as catalysts in Heck reactions. *Chem. Commun.* **1996**, 1921–1922.
- (20) Cvetovich, R. J.; Reamer, R. A.; DiMichele, L.; Chung, J. Y. L.; Chilenski, J. R. Unique tandem Heck–Lactamization naphthyridinone ring formation between acrylamides and halogenated pyridines. *J. Org. Chem.* **2006**, *71*, 8610–8613.
- (21) Taken from GSK solvent selection guide. <http://www.rsc.org/suppdata/gc/c0/c0gc00918k/c0gc00918k.pdf> (accessed September 12, 2013).
- (22) Wang, J.-L.; He, L.-N.; Miao, C.-X.; Li, Y.-N. Ethylene carbonate as a unique solvent for palladium-catalyzed Wacker oxidation using oxygen as the sole oxidant. *Green Chem.* **2009**, *11*, 1317–1320.
- (23) Schäffner, B.; Schäffner, F.; Verevkin, S. P.; Börner, A. Organic carbonates as solvents in synthesis and catalysis. *Chem. Rev.* **2010**, *110*, 4554–4581.
- (24) Bayardon, J.; Holz, J.; Schaffner, B.; Andrushko, V.; Verevkin, S. P.; Preetz, A.; Börner, A. Propylene carbonate as a solvent for asymmetric hydrogenations. *Angew. Chem., Int. Ed.* **2007**, *46*, 5971–5974.
- (25) Shaikh, A. G.; Sivaram, S. Organic carbonates. *Chem. Rev.* **1996**, *96*, 951–976.
- (26) Sakakura, T.; Kohno, K. The synthesis of organic carbonates from carbon dioxide. *Chem. Commun.* **2009**, 1312–1330.
- (27) Fischmeister, C.; Doucet, H. Greener solvents for ruthenium and palladium-catalyzed aromatic C–H bond functionalisation. *Green Chem.* **2011**, *13*, 741–753.
- (28) Eghbali, N.; Li, C.-J. Conversion of carbon dioxide and olefins into cyclic carbonates in water. *Green Chem.* **2007**, *9*, 213–215.
- (29) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. The solvatochromic comparison method. 6. The  $\pi^*$  scale of solvent polarities. *J. Am. Chem. Soc.* **1977**, *99* (18), 6027–6038.
- (30) Kamlet, M. J.; Abboud, J. L. M.; Abraham, M. H.; Taft, R. W. Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters,  $\pi^*$ ,  $\alpha$ , and  $\beta$ , and some methods for simplifying the generalized solvatochromic equation. *J. Org. Chem.* **1983**, *48* (17), 2877–2887.
- (31) Limberger, J.; Poersch, S.; Monterio, A. L. Pd-catalyzed Heck reactions of aryl bromides with 1,2-diarylethenes. *J. Braz. Chem. Soc.* **2011**, *22* (7), 1389–1394.
- (32) Batsanov, A. S.; Knowles, J. P.; Whiting, A. Mechanistic studies on the Heck–Mizoroki cross-coupling reaction of a hindered vinylboronate ester as a key approach to developing a highly stereoselective synthesis of a C1–C7 Z,Z,E-triene synthon for viridomycin. *J. Org. Chem.* **2006**, *72*, 2525–2532.
- (33) Fristrup, P.; Le Quemant, S.; Tanner, D.; Norrby, P.-O. Reactivity and regioselectivity in the Heck reaction: Hammett study of 4-substituted styrenes. *Organometallics* **2004**, *23*, 6160–6165.
- (34) Van Strijdonck, G. P. F.; Boele, M. D. K.; Kamer, P. C. J.; De Vries, J. G.; Van Leeuwen, P. W. N. M. Fast palladium catalyzed arylation of alkenes using bulky monodentate phosphorus ligands. *Eur. J. Inorg. Chem.* **1999**, 1073–1076.
- (35) Schmidt, A. F.; Smirnov, V. V.; Al-Halaiga, A. Kinetics of the Heck reactions of styrene with bromobenzene and iodobenzene in the presence of ligandless catalytic systems: A comparative study. *Kinet. Catal.* **2005**, *48* (3), 390–397.