Green Chemistry

PAPER

Cite this: Green Chem., 2013, 15, 490

Received 9th October 2012, Accepted 3rd December 2012 DOI: 10.1039/c2qc36584q

www.rsc.org/greenchem

Introduction

The Huisgen 1,3-dipolar cycloaddition of azides to alkynes has been recognized as one of the most attractive synthetic tools due to the convenient and reliable construction of 1,2,3-triazole derivatives, whose subunits are often found as a key nucleus of biologically active molecules.¹ The utility of the reaction has explosively increased since Sharpless and Meldal independently developed the regioselective synthetic method for the preparation of 1,4-disubstituted 1,2,3-triazoles using mono-substituted (terminal) alkynes and azides by the addition of a copper salt.^{2,3} The copper-catalyzed Huisgen cyclization is currently recognized as a representative of 'click chemistry,' the concept of which was established by Sharpless *et al.* for reliable reactions to efficiently produce functional materials.⁴

The development of the environmentally benign and costefficient protocols has been demanded from the view points of green sustainable chemistry. The use of heterogeneous transition metal catalysts is expected for possible reuse, since

monguchi@gifu-pu.ac.jp; Fax: +81 58 230 8109; Tel: +81 58 230 8109 ^bLaboratory of Molecular Science, Faculty of Engineering, Gifu University,

Solvent-free Huisgen cyclization using heterogeneous copper catalysts supported on chelate resins†

Yasunari Monguchi,^{*a} Kei Nozaki,^a Toshihide Maejima,^a Yutaka Shimoda,^a Yoshinari Sawama,^a Yoshiaki Kitamura,^b Yukio Kitade^{b,c} and Hironao Sajiki^{*a}

Copper catalysts supported on chelate resins bearing iminodiacetate moieties (DIAION CR11) or polyamine moieties (DIAION CR20) as chelating functional groups (12% Cu/CR11 and 7% Cu/CR20, respectively) were developed. 12% Cu/CR11 effectively catalyzed the Huisgen cycloaddition of mono-substituted alkynes to azides in the presence of triethylamine under totally solvent-free conditions to afford the corresponding 1,4-disubstituted 1,2,3-triazoles in excellent yields and in a completely regioselective manner. Furthermore, the Huisgen cycloaddition was found to effectively proceed without addition of triethylamine by the use of 7% Pd/CR20 as a catalyst.

> the metal particles are embedded on the supports.⁵ The elimination of solvents from the reaction mixture is also an important issue, leading to the significant reduction of solvent wastes and the size of the synthetic equipment and/or manufacturing plants.⁶ During the course of our study to establish environmentally and economically responsible methods in organic chemistry, the solvent-free hydrogenation and the Suzuki–Miyaura reaction catalyzed by palladium on carbon as a heterogeneous catalyst have recently been reported.⁷

> Application of copper catalysts immobilized on supports for the Huisgen cyclization of azides to alkynes has been demonstrated.8 The supports employed to date are activated carbon,9 inorganic materials, such as zeolites,¹⁰ amine-bound silica,¹¹ superparamagnetic mesoporous silica,¹² AlO(OH),¹³ metal oxide,¹⁴ and hydrotalcite,¹⁵ an ionic liquid,¹⁶ a ligand-bound organic polymer,¹⁷ a polysaccharide,¹⁸ and an ion exchange resin, such as Amberlyst A2119 and Dowex.20 The catalysts supported on these materials require multiple steps to prepare, in most cases, and centrifugation or decantation to separate them from the reaction mixture in some cases. Copper oxide on acetylene carbon black^{9d} and copper on Amberlyst A21^{19b} were only employed for the solvent-free Huisgen cyclizations. The former catalyst could be reused for at least five cycles, but microwave conditions were adopted and centrifugation is required for the separation from the reaction mixture. The reuse is not even mentioned in the latter case. A non-supported copper metal organic framework also catalyzed the solvent-free Huisgen cyclization, but excess amounts of catalyst (10 mol%) and acetylene (12 equiv.) were used.^{8c}

> We recently developed a copper catalyst supported on a commercial synthetic adsorbent, DIAION HP20 (Mitsubishi Chemical Corporation),^{21,22} which is a polystyrene-divinyl-benzene-based polymer with a relatively large pore size (radius

View Article Online

^aLaboratory of Organic Chemistry, Gifu Pharmaceutical University, 1-25-4

Daigaku-nishi, Gifu 501-1196, Japan. E-mail: sajiki@gifu-pu.ac.jp,

Eaboratory of Molecular Science, Faculty of Engineering,

¹⁻¹ Yanagido, Gifu 501-1193, Japan

^cUnited Graduate School of Drug Discovery and Medicinal Information Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

 $[\]dagger$ Electronic supplementary information (ESI) available: Scanning transmission electron microscopy (STEM) images, electron probe microanalysis (EPMA) data, and X-ray photoelectron spectroscopy (XPS) spectra of 12% Cu/CR11 and 7% Cu/CR20, detailed procedure and results of reuse test of catalysts, spectral data of products, and ¹H and ¹³C NMR spectra of new products. See DOI: 10.1039/c2gc36584g

approximately 260 Å) and area (approximately 590 m² g⁻¹), with an expectation of its stable supply and strong activity. Although only one weight% of copper ions was embedded on the catalyst, the Huisgen cycloaddition of azides to alkynes heterogeneously proceeded in toluene at room temperature.²³

Chelate resins, DIAION CR11 and DIAION CR20 (Mitsubishi Chemical Corporation), polystyrene-divinylbenzene-based polymers possessing iminodiacetic acid moieties and polyamine moieties as the ligands, respectively, can capture various metal ions by their chelating abilities, and have been used to remove heavy metal ions from water.²⁴ These resins should also be guaranteed as industrial products in quality and properties due to the advanced product control under the strict regulations. Therefore, we expected that highly loaded copper catalysts supported on DIAION CR11 and CR20 with reliable quality could be readily produced by the rigid complexation.

Results and discussion

Preparation of 12% Cu/CR11 and 7% Cu/CR20

Copper ion was immobilized by immersing DIAION CR11 in an aqueous solution of $Cu(NO_3)_2 \cdot 3H_2O$ at room temperature for 4 h. The resulting light blue solids were collected by filtration, washed with water and MeOH, then dried under reduced pressure to give copper on DIAION CR11 (Cu/CR11) (Scheme 1). The inductively coupled plasma-atomic emission spectrometry (ICP-AES) of the Cu/CR11 showed that 12 wt% copper species were embedded on the DIAION CR11. DIAION CR20 was treated with an aqueous solution of Cu(NO₃)₂·3H₂O in accordance with the procedure for the preparation of 12% Cu/CR11 to afford 7% Cu/CR20.²⁵

12% Cu/CR11-catalyzed Huisgen cyclization

The 12% Cu/CR11-catalyzed Huisgen cyclization of benzylazide with ethynylbenzene (1.1 equiv.) in the presence of Et_3N (0.22 equiv.) was examined in heated H_2O (70 °C). The reaction efficiency and regioselectivity were remarkably enhanced with the escalating use of 12% Cu/CR11 (Table 1, entries 1–4), and complete regioselectivity was achieved using more than 1 mol% of 12% Cu/CR11 to give 1,4-disubstituted 1,2,3-triazole as the sole product after a 10 h reaction (entries 3 and 4). Although 12% Cu/CR11 (1 mol%) poorly catalyzed the reaction in MeOH or toluene (entries 5 and 6), it was completed within 4 h even without solvents contrary to our expectation (entry 7). The application of heat is effective for the reaction progress (entries 7–10), but the effect was virtually the same at higher than 70 °C (entries 7 and 10).

The solvent-free 1,3-dipolar cycloaddition of ethynylbenzene with benzylazide was markedly impeded in the

DIAION CR11 + _____ washing/dryness → 12% Cu/CR11 Cu(NO₃)₂·3H₂O in H₂O rt, 4 h

Scheme 1 Preparation of 12% Cu/CR11.

 Table 1
 Solvent effect on the 12% Cu/CR11-catalyzed cycloaddition of benzylazide with ethynylbenzene

$Bn-N_3 + \parallel$	12% Cu/CR11 Et ₃ N (0.22 equiv) ► 10 h	Bn N +	Bn N N
1 (1.1 equiv)		2 Ph	3

$\begin{array}{c ccccccccccccccccccccccccccccccccccc$						
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Entry	12% Cu/CR11 (mol%)	Solvent	Temp (°C)	Time (h)	Ratio ^{<i>a</i>} 1:2:3
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1	0	H_2O	70	10	55:28:17
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2	0.5	H_2O	70	10	7:86:7
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3	1	H_2O	70	10	3:97:0
5 1 MeOH 70 10 21:79:0 6 1 Toluene 70 10 65:35:0 7 1 Neat 70 4 0:100: 8 1 Neat rt 24 20:80:0 9 1 Neat 50 24 0:100: 10 1 Neat 80 4 0:100:	4	3	H_2O	70	10	0:100:0
6 1 Toluene 70 10 65:35:0 7 1 Neat 70 4 0:100: 8 1 Neat rt 24 20:80:0 9 1 Neat 50 24 0:100: 10 1 Neat 80 4 0:100:	5	1	MeOH	70	10	21:79:0
7 1 Neat 70 4 0:100: 8 1 Neat rt 24 20:80:0 9 1 Neat 50 24 0:100: 10 1 Neat 80 4 0:100:	6	1	Toluene	70	10	65:35:0
8 1 Neat rt 24 20:80:0 9 1 Neat 50 24 0:100: 10 1 Neat 80 4 0:100:	7	1	Neat	70	4	0:100:0
9 1 Neat 50 24 0:100: 10 1 Neat 80 4 0:100:	8	1	Neat	rt	24	20:80:0
10 1 Neat 80 4 0:100:	9	1	Neat	50	24	0:100:0
	10	1	Neat	80	4	0:100:0

^{*a*} Determined by ¹H NMR.

 Table 2
 Effect of catalytic amounts of additives on the 12% Cu/CR11-catalyzed cycloaddition of benzylamine with ethynylbenzene

	Bn-N ₃ + Ph 12% Cu/CR11 (1 mol%) Addituve Neat, 70 °C, 4 h	Bn N N N Ph	Bn N N N	
	1 (1.1 equiv)	2	3	
			Ratio ^a	
Entry	Additive	Equiv.	1:2:3	
1	None	_	67:19:14	
2	Et_3N	0.22	$0:100(98)^b:0$	
3	Tri- <i>n</i> -butylamine	0.22	15:83:2	
4	Diethyl amine	0.22	0:100:0	
5	Ethylenediamine	0.22	74:16:10	
6	Pyridine	0.22	77:15:8	
7	Aniline	0.22	78:15:7	
8	1,10-Phenanthroline	0.22	81:10:9	
9	Na_2CO_3	0.22	71:18:11	
10	NaHCO ₃	0.22	$0:100(95)^b:0$	
11	Cs_2CO_3	0.22	73:16:11	
12	Ascorbic acid	0.22	79:10:11	
13	Sodium ascorbate	0.22	45:55:0	
14	Et_3N	0.11	42:58:0	
15	Et ₃ N	0.55	0:100:0	

^a Determined by ¹H NMR. ^b Isolated yield.

absence of Et_3N (Table 2, entry 1). The addition of Et_3N , *n*-Bu₃N, Et_2NH , or NaHCO₃ was found to accelerate the reaction progress (entries 2, 3, 4, and 10), while other nitrogen-containing bases and inorganic bases showed no positive effects on both the conversion and regioselectivity (entries 5–9 and 11). The addition of ascorbic acid or its sodium salt as a reducing agent of Cu^{II} to Cu^I poorly promoted the reaction (entries 12 and 13).³ As a result, Et_3N was selected as the optimal additive due to the lower nucleophilicity compared to Et_2NH and NaHCO₃, which achieved a 100% conversion to the 1,4-disubstituted triazole (2). The reaction smoothly proceeded using





^{*a*} Isolated yield.^{*b*} A mixture of the starting azide, 1,4-disubstituted triazole, and 1,5-disubstituted triazole was obtained in the ratio of 33:57:6, respectively (¹H NMR spectrum of the crude materials).

only 0.22 equiv. of Et_3N , and 2 was regioselectively obtained in a quantitative conversion yield (entries 2 *vs.* 14 and 15).

The results of the 12% Cu/CR11-catalyzed solvent-free Huisgen cyclization of ethynylbenzene (1.1 equiv.) with a variety of azides in the presence of Et₃N (0.22 equiv.) are shown in Table 3. When the reaction did not effectively proceed with 1 mol% of 12% Cu/CR11, the reaction efficiency was improved by the escalating use of the catalyst up to 5 mol% (entries 3-8). While the reaction of 4-fluorobenzylazide using 1 mol% of 12% Cu/CR11 afforded a mixture of the unreacted azide, the desired 1,4-substituted triazole, and the undesired 1,5-disubstituted triazole (entry 2), the reaction efficiency was significantly improved with an increase in the use of 12% Cu/CR11 to 3 mol%, and the 1,4-disubstituted triazole was obtained in 88% yield as the sole product (entry 3). Arylmethylazides (entries 1, 3, and 4), arylazides (entries 5-8), and alkylazides (entries 9 and 10) could react with ethynylbenzene in a solvent-free fashion to produce the corresponding 1,4-disubstituted triazoles in excellent yields.

Both aryl- (Table 4, entries 1 and 2) and alkylalkynes (entries 3–6) were good substrates for the solvent-free cycloaddition with benzyl azide. However, the reaction of ethyl 2-propynoate with benzyl azide afforded a complex mixture



Entry	R	12% Cu/CR11 (mol%)	Time (h)	Yield ^a (%)
1	Me	1	4	92
2	MeO-	5	2	84
3	<i>n</i> -Pr	5	8	99
4	<i>n</i> -Bu	5	8	88
5	<i>n</i> -Pentyl	5	8	88
6	n-Hexyl	5	8	94
7	EtO ₂ C	1	4	b
8	EtO ₂ C	1	2	94 ^c
9	EtO ₂ C	1	3	95^d

^{*a*} Isolated yield. ^{*b*} Complex mixture. ^{*c*} Obtained as a mixture of regioisomers (1,4-/1,5-substituted triazoles = 86:14) without base. ^{*d*} NaHCO₃ was used instead of Et₃N, and the 1,4-disubstituted triazole was obtained as the sole product.

(entry 7),²⁶ and a mixture of 1,4-disubstituted and 1,5-disubstituted triazoles was obtained in the ratio of 86 : 14 without Et_3N (entry 8). The poor regioselectivity was completely overcome by the use of NaHCO₃ as a base (entry 9), as is the case of the cycloaddition of ethynylbenzene with benzyl azide (Table 2, entry 10). The 12% Cu/CR11-catalyzed Huisgen cycloaddition was therefore established as a general method for the preparation of the 1,4-disubstituted 1,2,3-triazole under solvent-free conditions.

7% Cu/CR20-catalyzed Huisgen cyclization

Since the 7% Cu/CR20 possesses chelating polyamino moieties within DIAION CR20 as the support, the reaction was expected to proceed without the addition of Et_3N . As expected, the reaction of benzylazide and ethynylbenzene was smoothly completed at 70 °C together with a complete regioselectivity in a solvent-free manner in the absence of Et_3N (Table 5, entries 1 and 2). Further optimization of the reaction conditions revealed that 1 mol% of 7% Cu/CR20 loading and 70 °C of heat were necessary for the smooth reaction (entries 3–6).

A variety of 1,4-disubstituted 1,2,3-triazoles was synthesized using 7% Cu/CR20 at 70 °C under neat conditions (Table 6). Although linear alkyl substituted azides and alkynes were slightly less reactive as substrates, the reaction efficiencies were improved by the increase of the catalyst usage and prolonged reaction time (entries 6, 9, and 10).

Reuse test of 12% Cu/CR11 and 7% Cu/CR20

The reuse test of 12% Cu/CR11 was next examined (Table 7). The catalyst was effectively recovered from the reaction mixture until the 4th run. The recovered amounts of the catalyst significantly decreased after the 5th run due to the difficulty of the catalyst removal from the filtering paper because of the

Table 5 Optimization for the solvent-free 7% Cu/CR20-catalyzed cycloaddition of benzylazide with ethynylbenzene



Entry	7% Cu/CR20 (mol%)	Temp (°C)	Ratio ^{a} 1 :2:3
1^b	1.0	70	0:100:0
2	1.0	70	0:100:0
3	0.50	70	22:74:4
4^c	1.0	rt	73:27:0
5	1.0	60	1:99:0
6	1.0	80	0:100:0

^a Determined by ¹H NMR. ^b Et₃N was added as the additive. ^c The reaction was carried out for 24 h.

Table 6 7% Cu/CR20-catalyzed solvent-free Huisgen cyclization between various alkynes and azides

	$R^{1}-N_{3}$ +	2 ² 7% Cu/CF Neat, 70 equiv)	$R^{20} \xrightarrow{R^{1}} N$	R ²	
Entry	R ¹	\mathbb{R}^2	7% Cu/ CR20 (mol%)	Time (h)	Yield ^a (%)
1 2	Bn MeO	Ph Ph	1 1	4 4	93 96
3	EtO ₂ C	Ph	5	4	90
4	MeO	Ph	7	4	87
5	\bigcirc	Ph	1	10	95
6 7	Me(CH ₂) ₅ Bn	Ph Me	7 1	12 3	98 86
8	Bn	MeO	1	4	92
9 10 ^a Isolat	Bn Bn	<i>n-</i> Bu <i>n-</i> Hexyl	7 7	12 10	72 68
isoiat	isolateu yielu.				

reduction of the catalyst particle size by the mechanical damage during stirring. The catalyst could be used until the 4th run without any significant catalyst activity loss, while it decreased in the 5th run presumably due to the physical destruction of the catalyst and leaching of copper species from the catalyst into the solvents used for washing during the work-up process. The concentration of the copper species was then measured after the addition of solvent to the reaction

able 7 Reuse test of 12% C	Cu/CR11
----------------------------	---------

	$Bn-N_3 + \begin{vmatrix} Ph & 1\\ H & - \end{vmatrix}$ (1.1 equiv)	2% Cu/CR11 (1 mol%) it ₃ N (0.22 equiv) Neat, 70 °C, 4 h	Bn N N Ph
Run	Recovered cat	alyst (%)	Yield of triazole ^{a} (%)
1	100		97
2	96		98
3	94		98
4	94		99
5	88		$74(21^{b})$

^{*a*} Isolated yield. ^{*b*} Recovered starting azide.

Table 8 Reuse test of 7% Cu/CR20

	$Bn-N_3 + \parallel$	7% Cu/CR20 (1 mol%) Neat, 70 °C, 5 h	Bn N N N Ph
Run	Recovered	l catalyst (%)	Yield of triazole ^{a} (%)
1	100		100
2	100		99
3	96		100
4	98		100
5	92		100
^a Isolated	l yield.		

mixture to remove the catalyst by filtration, and approximately 3.0% of copper species was leached out from the 12% Cu/CR11.

The reuse test of 7% Cu/CR20 was also conducted using the cycloaddition of benzylazide with ethynylbenzene (Table 8). No decrease in the catalytic activity was observed until at least the 5th run, and the desired triazole was quantitatively obtained at each run.

Conclusions

In summary, we developed novel copper catalysts, 12% Cu/CR11 and 7% Cu/CR20, supported on commercially available chelate resins possessing iminodiacetic acid moieties and polyamine moieties, respectively, as the chelating functionalities. The preparation method of 12% Cu/CR11 and 7% Cu/CR20 only requires soaking the chelate resins in a stirring aqueous solution of Cu(NO₃)₂·3H₂O. 12% Cu/CR11 effectively catalyzed the Huisgen cyclization of azides to alkynes in the presence of a catalytic amount of Et₃N under the solvent-free conditions, and a variety of 1,4-disubstituted 1,2,3-triazoles were obtained in excellent yields. The solvent- and Et₃N-free Huisgen cyclization was also established by the use of 7% Cu/CR20 as a catalyst. 12% Cu/CR11 and 7% Cu/CR20 could be reused several times without any significant reduction of the

catalyst activity. A further study is currently underway in our laboratory to expand the utility of the 12% Cu/CR11 and 7% Cu/CR11 as the heterogeneous catalysts used for reactions other than Huisgen reaction.

Experimental

General

All reagents and solvents were obtained from commercial sources and used without further purification. The DIAION CR11 and CR20 were obtained from Mitsubishi Chemical Corporation (Japan). Flash column chromatography was performed using silica gel 60N [spherical neutral (63-210 µm)] from Kanto Chemical Co., Inc. The ¹H and ¹³C NMR spectra were recorded by a JEOL JNM AL-400 (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR). Chemical shifts (δ) are expressed in parts per million and internally referenced [0.00 ppm for tetramethylsilane (TMS)/CDCl₃ for ¹H NMR and 77.0 ppm for CDCl₃ for ¹³C NMR]. The mass spectra were taken by JEOL JMS Q1000GC Mk II Quad GC/MS for EI and JEOL JMS-T100TD for ESI. All products were characterized by their ¹H and ¹³C NMR and mass spectra (and high resolution mass spectra for two new compounds). The spectral data for all known compounds were identical to those in the literature, see ESI.[†]

Preparation of 12% Cu/CR11

DIAION CR11 (100 g) was added to an aqueous solution (400 mL) of Cu(NO₃)₂·3H₂O (24.2 g, 100 mmol), and the mixture was gently stirred at room temperature for 4 h. The resulting blue solid was collected on a Kiriyama funnel (Kiriyama Glass Co., Ltd, Tokyo, Japan), washed with H₂O (200 mL) and MeOH (200 mL), and dried under reduced pressure for 12 h to produce the Cu/CR11 (54.5 g). The inductively coupled plasma-atomic emission spectrometry (ICP-AES) revealed that copper ions were immobilized at 12 wt% concentration on CR11.

Preparation of 7% Cu/CR20

Cu/CR20 was similarly prepared from DIAION CR20 and Cu(NO₃)₂· $3H_2O$, and the concentration of copper ions of Cu/CR20 was determined as 7 wt% by ICP-AES.

Typical procedure of 12% Cu/CR11-catalyzed, solvent-free Huisgen cyclization

A mixture of the azide (500 µmol), the alkyne (550 µmol), Et₃N (15.4 µL, 220 µmol), and 12% Cu/CR11 (2.6 mg, 5.00 µmol) in a test tube was stirred at 70 °C for the specified time. CH_2Cl_2 (10 mL) was added, and the mixture was then filtered. To the filtrate was added H₂O (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layers were washed with brine (10 mL × 2), dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the corresponding 1,4-disubstituted 1,2,3-triazole.

Typical procedure of 7% Cu/CR20-catalyzed, solvent-free Huisgen cyclization

A mixture of the azide (500 µmol), the alkyne (550 µmol), and 7% Cu/CR20 (4.5 mg, 5.00 µmol) in a test tube was stirred at 70 °C for the specified time. CH_2Cl_2 (10 mL) was added, and the mixture was then filtered. To the filtrate was added H₂O (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layers were washed with brine (10 mL × 2), dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the corresponding 1,4-disubstituted 1,2,3-triazole.

Acknowledgements

We sincerely thank the Mitsubishi Chemical Corporation for the gift of DIAION CR11. We also thank the N.E. Chemcat Corporation for the SEM, EPMA, and ICP-AES measurements.

Notes and references

- (a) R. Huisgen, G. Szeimies and L. Moebius, *Chem. Ber.*, 1967, **100**, 2494–2507; (b) R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padowa, Wiley, New York, 1984, pp. 1–176.
- 2 (a) C. W. Tornøe, C. Christensen and M. Meldal, J. Org. Chem., 2002, 67, 3057–3064; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, Angew. Chem., 2002, 114, 2708–2711, (Angew. Chem., Int. Ed., 2002, 41, 2596–2599).
- For reviews: (a) V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51–68; (b) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, 108, 2952–3015.
- 4 (a) H. C. Kolb, M. G. Finn and K. B. Sharpless, Angew. Chem., 2001, 113, 2056–2075, (Angew. Chem., Int. Ed., 2001, 40, 2004–2021); (b) H. C. Kolb and K. B. Sharpless, Drug Discovery Today, 2003, 8, 1128–1137.
- 5 (a) L. Yin and J. Liebscher, *Chem. Rev.*, 2007, 107, 133–173;
 (b) M. J. Climent, A. Corma and S. Iborra, *Chem. Rev.*, 2011, 111, 1072–1133.
- 6 (a) Solvent-free Organic Synthesis, ed. K. Tanaka, 2nd edn, Wiley-VCH, Weinheim, 2008; (b) Topics Current Chemistry 254, Organic Solid State Reactions, ed. F. Toda, Springer, Berlin, 2005; (c) D. C. Dittmer, Chem. Ind., 1997, 19, 779– 784; (d) R. S. Varma, Green Chem., 1999, 1, 43–55; (e) K. Tanaka and F. Toda, Chem. Rev., 2000, 100, 1025– 1074; (f) R. S. Varma, Pure Appl. Chem., 2001, 73, 193–198; (g) P. J. Walsh, H. Li and C. A. de Parrodi, Chem. Rev., 2007, 107, 2503–2545; (h) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol and P. Machado, Chem. Rev., 2009, 109, 4140–4182.
- 7 Y. Monguchi, Y. Fujita, S. Hashimoto, M. Ina, T. Takahashi,
 R. Ito, K. Nozaki, T. Maegawa and H. Sajiki, *Tetrahedron*, 2011, 67, 8628–8634.

- 8 For non-supported heterogeneous copper catalysts:
 (a) S. K. Yousuf, D. Mukherjee, B. Singh, S. Maity and S. C. Taneja, *Green Chem.*, 2010, 12, 1568–1572;
 (b) B. R. Buckley, S. E. Dann, D. P. Harris, H. Heaney and E. C. Stubbs, *Chem. Commun.*, 2010, 46, 2274–2276;
 (c) I. Luz, F. X. L. i Xamena and A. Corma, *J. Catal.*, 2010, 276, 134–140.
- 9 (a) B. H. Lipshuz and B. R. Taft, Angew. Chem., 2006, 118, 8415-8418, (Angew. Chem., Int. Ed., 2006, 45, 8235-8238); (b) P. Cintas, K. Martina, B. Robaldo, D. Garella, L. Boffa and G. Cravotto, Collect. Czech. Chem. Commun., 2007, 72, 1014-1024; (c) H. Sharghi, R. Khalifeh and M. M. Doroodmand, Adv. Synth. Catal., 2009, 351, 207-218; (d) H. Kang, H. J. Lee, J. C. Park, H. Song and K. H. Park, Top. Catal., 2010, 53, 523-528; (e) F. Alonso, Y. Noglie, G. Radivoy and M. Yus, Org. Biomol. Chem., 2011, 9, 6385-6395.
- 10 (a) S. Chassaing, M. Kumarraja, A. S. S. Sido, P. Pale and J. Sommer, Org. Lett., 2007, 9, 883–886; (b) A. Alix, S. Chassaing, P. Pale and J. Sommer, Tetrahedron, 2008, 64, 8922–8929; (c) S. Chassaing, A. S. S. Sido, A. Alix, M. Kumarraja, P. Pale and J. Sommer, Chem.–Eur. J., 2008, 14, 6713–6721; (d) S. Chassaing, A. Alix, T. Boningari, K. S. S. Sido, M. Keller, P. Kuhn, B. Louis, J. Sommer and P. Pale, Synthesis, 2010, 1557–1567; (e) V. Bénéteau, A. Olmos, T. Boningari, J. Sommer and P. Pale, Tetrahedron Lett., 2010, 51, 3673–3677.
- 11 (a) T. Miao and L. Wang, *Synthesis*, 2008, 363–368;
 (b) T. Shamin and S. Paul, *Catal. Lett.*, 2010, **136**, 260–265;
 (c) P. Veerakumar, M. Velayudham, K.-L. Lu and S. Rajagopal, *Catal. Sci. Technol.*, 2011, **1**, 1512–1525.
- 12 B. S. Lee, M. Yi, S. Y. Chu, J. Y. Lee, R. Kwon, K. R. Lee, D. Kang, W. S. Kim, H. B. Lim, J. Lee, H.-J. Youn, D. Y. Chi and N. H. Hur, *Chem. Commun.*, 2010, 46, 3935–3937.
- 13 I. S. Park, M. S. Kwon, Y. Kim, J. S. Lee and J. Park, *Org. Lett.*, 2008, **10**, 497–500.
- 14 (a) T. Katayama, K. Kamata, K. Yamaguchi and N. Mizuno, *ChemSusChem*, 2009, 2, 59–62; (b) K. Yamaguchi, T. Oishi, T. Katayama and N. Mizuno, *Chem.-Eur. J.*, 2009, 15, 10464–10472.
- 15 K. Namitharan, M. Kumarraja and K. Pitchumani, *Chem.-Eur. J.*, 2009, **15**, 2755–2758.
- 16 H. Hagiwara, H. Sasaki, T. Hoshi and T. Suzuki, *Synlett*, 2009, 643–647.

- 17 (a) M. Lammens, J. Skey, S. Wallyn, R. O'Reilly and F. D. Prez, *Chem. Commun.*, 2010, 46, 8719–8721;
 (b) Z. Zhang, C. Dong, C. Yang, D. Hu, J. Long, L. Wang, H. Li, Y. Chen and D. Kong, *Adv. Synth. Catal.*, 2010, 352, 1600–1604; (c) Y. M. A. Yamada, S. M. Sarkar and Y. Uozumi, *J. Am. Chem. Soc.*, 2012, 134, 9285–9290;
 (d) T. Suzuka, Y. Kawahara, K. Ooshiro, T. Nagamine, K. Ogihara and M. Higa, *Heterocycles*, 2012, 85, 615–626.
- 18 A. Kumar, S. Aerry, A. Saxena, A. De and S. Mozumdar, *Green Chem.*, 2012, 14, 1298–1301.
- 19 (*a*) C. Girard, E. Önen, M. Aufort, S. Beauvière, E. Samson and J. Herscovici, *Org. Lett.*, 2006, 8, 1689–1692; (*b*) I. Jlalia, F. Meganem, J. Herscovici and C. Girard, *Molecules*, 2009, 14, 528–539.
- 20 U. Sirion, Y. J. Bae, B. S. Lee and D. Y. Chi, *Synlett*, 2008, 2326–2330.
- 21 T. Adachi, S. Ando and J. Watanabe, *J. Chromatogr.*, *A*, 2002, **944**, 41–59.
- 22 For palladium on DIAION HP20, see: (a) Y. Monguchi,
 Y. Fujita, K. Endo, S. Takao, M. Yoshimura, Y. Takagi,
 T. Maegawa and H. Sajiki, *Chem.-Eur. J.*, 2009, 15, 834–837;
 (b) Y. Monguchi, K. Sakai, K. Endo, Y. Fujita, M. Niimura,
 M. Yoshimura, T. Mizusaki, Y. Sawama and H. Sajiki, *ChemCatChem*, 2012, 4, 546–558.
- 23 Y. Kitamura, K. Taniguchi, T. Maegawa, Y. Monguchi, Y. Kitade and H. Sajiki, *Heterocycles*, 2009, 77, 521–532.
- 24 (a) Home page for DIAION of Mitsubishi Chemical Co., see http://www.diaion.com/Index_E.htm; (b) R. Koivula, J. Lehto, L. Pajo, T. Gale and H. Leinonen, *Hydrometallurgy*, 2000, 56, 93–108; (c) A. Cavaco, S. Fernandes, M. M. Quina and L. M. Ferreira, J. Hazard. Mater., 2007, 144, 634–638; (d) S. A. Cavaco, S. Fernandes, C. M. Augusto, M. J. Quina and L. M. Gando-Ferreira, J. Hazard. Mater., 2009, 169, 516–523; (e) L. M. Gando-Ferreira, I. S. Romao and M. J. Quina, Chem. Eng. J., 2011, 172, 277–286.
- 25 The scanning transmission electron microscopy (STEM) images, electron probe microanalyses (EPMA), and X-ray photoelectron spectroscopy (XPS) spectra are shown in the supplementary data.
- 26 Although the copper-catalyzed homo-coupling (Glaser coupling) or/and polymerization of ethynylbenzene based on the acidic alkyne hydrogen strongly activated by the electron-withdrawing ester moiety might have taken place, the identification of each of the products was impossible because of the excessive complexity of the reaction.