

# Graphite as an effective catalyst for Michael addition of indoles to nitroolefins in aqueous alcoholic solution

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**Abstract** Graphite effectively catalyzes the Michael addition of indole and 2-methylindole to nitroolefins in aqueous alcoholic solution at room temperature to afford the corresponding adduct.

**Keywords** Indole · Nitroolefin · Michael addition · Graphite · Catalyst

## Introduction

The Friedel–Crafts alkylation of aromatic compounds is one of the most important methods for the introduction of a substituent on an aromatic compound. However, it is associated with a problem of polyalkylation and formation of rearranged products. In electron-rich heterocycles like indole, the problem of polyalkylation is mitigated by the preference of 3-position over 2-position to undergo alkylation. However, many of the conventional catalysts are intolerable to such electron-rich heterocycles due to the propensity with which they tend to undergo oligomerization. So, there is a continuous search for milder reagents which would avoid such complications. Further impetus is provided by green chemistry towards development of environmentally benign processes.

3-Substituted indoles have been target of synthesis due to the presence of this motif in large number of indole derivatives [1–3] and biologically active compounds [4–6]. The conjugate addition of indoles to nitroolefins has attracted considerable attention due to the versatility with which the nitro group can be transformed [7, 8] into other functional

groups. Several catalysts are used for this purpose such as Yb(OTf)<sub>3</sub> [9], InCl<sub>3</sub> [10], InBr<sub>3</sub> [8], Sc(OTf)<sub>3</sub> [11], bis-arylureas or bis-arylthioureas [12], SmI<sub>3</sub> [13], [Al(DS)<sub>3</sub>·3H<sub>2</sub>O [14], CeCl<sub>3</sub>·7H<sub>2</sub>O [15, 16], I<sub>2</sub> [17], thio-urea-based organocatalyst [18], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [19], Zn(OTf)<sub>2</sub> [20], basic alumina [21], silica-sulfuric acid [22], sulfamic acid [23], carbohydrate-based tolylsulfonylhydrazine [24], NBS [25], tetrabutylammonium hydrogen sulfate [26], and silanediol [27]. Catalyst-free aqueous [28], solvent-free [29, 30], and microwave methods [31–33] are also reported. Asymmetric version using chiral metal and organocatalyst is also known [34, 35]. Recently graphite oxide is reported for addition of indole to nitrostyrenes in H<sub>2</sub>O/THF solvent to deliver the products in moderate yields [36].

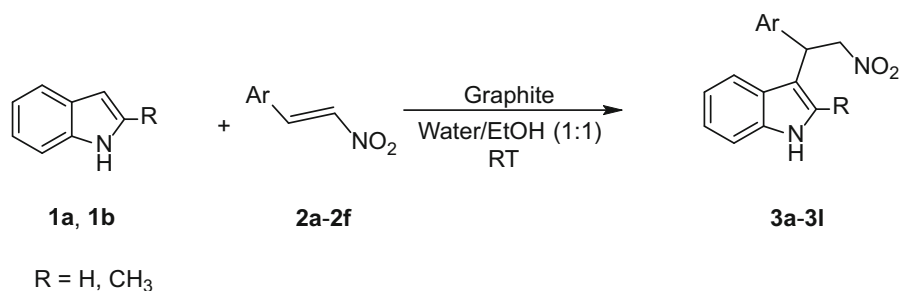
Although the Michael addition of nucleophilic indoles to nitroalkenes has been well studied, the area is far from fully explored. Environmental concerns in research and industry are increasing with the increasing pressure to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by ever more strict laws. Hence, the challenge for a sustainable environment calls for the use of clean procedures to avoid the use of harmful reagents and solvents. In recent years, graphite has found its use in organic transformations. It is found to be an effective catalyst for Friedel–Craft alkylation [37, 38], benzylation of aromatic compounds and Diels–Alder reaction [39], cleavage of ethers by acyl halides [40], conversion of aldehydes into nitriles [41], and oxidation [42, 43]. It is also reported for hydrogenation of olefins using potassium graphite intercalates [44].

## Results and discussion

As a part of our interest [45] in green chemistry, recently we used graphite as a catalyst for the synthesis of

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Scheme 1



quinoxalines [46]. Taking into consideration its ability to act as a catalyst, we thought to exploit it for the Michael-type additions of indoles to electron-deficient olefins. In our efforts, initially we tried the reaction of indole with nitrostyrene in ethanol on 1 mmol scale. Checking (TLC) that no reaction takes place by stirring, to the reaction mixture we added 100 mg (~40 wt%) of graphite (flakes, Aldrich chemicals) and continued stirring it further. However, after prolonged stirring, we could not notice (TLC) any product formation. Next, we tried the reaction in other solvents like dioxane, dichloromethane, chloroform, toluene, THF, and methanol in presence of graphite. In none of these cases, we could observe (TLC) any product formation. Further, we attempted the reaction in water (universal solvent) where we found that the reaction does take place (TLC), however, it could not go to completion as reaction mass was sticking to the stirring bar due to insolubility of reactants and product in the medium. The observation of formation of product suggested that indeed graphite is acting as a catalyst. To further confirm this observation, reaction in water without graphite was repeated where after prolonged stirring, we could observe trace amount of product formation. This suggested that for the reaction to take place, water is essential and graphite is accelerating the reaction. So, we tried the reaction in different ratio of water miscible solvents (THF–water, dioxane–water, methanol–water, and ethanol–water). The ideal solvent water combination ratio was found to be 1:1 where the reaction mixture remained homogenous and the reaction could go to completion (TLC, after consumption of nitrostyrene) in a shorter time. Considering the toxicity and the price of the solvents, we chose ethanol–water solvent combination for further study. Next, the effect of catalyst loading was investigated. For 1 mmol of indole and 1.1 mmol of nitrostyrene, when 25 mg (~10 wt%) of graphite was used reaction took 15.0 h for completion. But when graphite quantity was increased to 50 mg (~20 wt%), the reaction got completed in 12.0 h. Further increase in graphite quantity did not reduce the reaction time further.


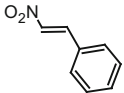
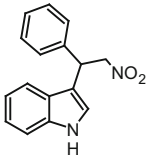

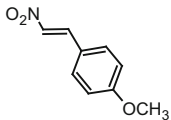
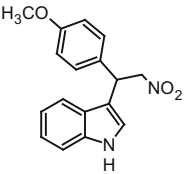

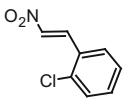
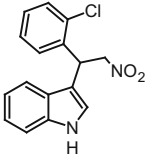

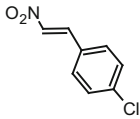
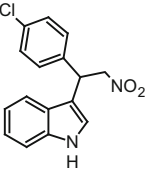

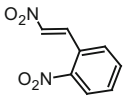
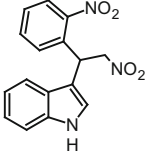

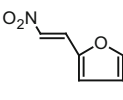
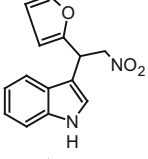
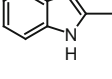
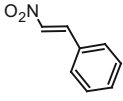
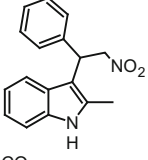
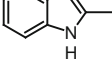
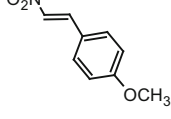
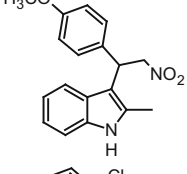
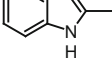
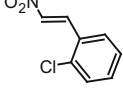
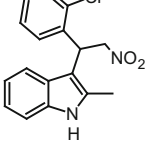
Using this protocol indole (**1a**) was treated with various nitrostyrenes **2a–2f** with electron-donating as well as electron-withdrawing groups successfully (Scheme 1; Table 1). Parent nitrostyrene (**2a**) gave the desired product **3a** in 61 % yield in 7 h. Nitrostyrene **2b** with electron-donating methoxy group provided good yield of product **3b** in 12 h whereas nitrostyrene **2d** with electron-withdrawing chloro group underwent Michael addition to form adduct **3d** at a faster rate resulting in similar yield. Similarly, other substituted nitrostyrenes **2c–2f** reacted to deliver the desired products **3c–3f** in moderate to good yields. Likewise, 2-methylindole (**1b**) reacted with nitrostyrenes **2a–2f** to give the corresponding adducts **3g–3l** in moderate to good yields. Nitrostyrene **2b** with electron-donating group showed the product **3h** formation in 40 min in 64 % yield whereas nitrostyrene **2d** with electron-withdrawing group in slightly reduced time gave 66 % yield of the desired product **3j**. As expected 2-methylindole reacts faster and gives comparatively better yield than the parent indole. Further, this protocol was also extended successfully for dimethyl acetylenedicarboxylate (**2g**) (Scheme 2). Both **1a** and **1b** reacted smoothly in short period of time to furnish the desired Michael adducts **3m, 3n** in good yields. In absence of graphite, trace amount of product formation (TLC) was seen after prolonged stirring.

The recyclability of the catalyst, i.e., graphite was also studied for four cycles for the reaction between 2-methylindole and nitrostyrene **2b** (Scheme 3; Table 2).

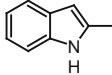
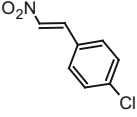
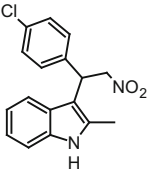
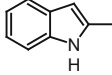
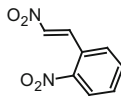
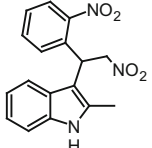
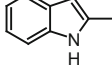
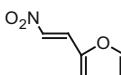
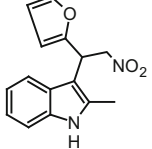
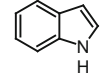
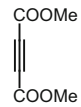
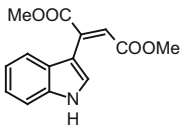
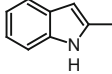
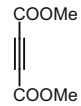
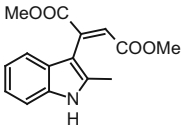
The exact role of graphite in the present protocol is not clearly understood; probably the  $\pi$ -stacking of nitroolefins on the graphite layer takes place followed by the attack of indole on the graphite-nitroolefins adduct as postulated by Acocella et al. [47]. Further support for this mechanism can be obtained by the fact that the reaction of indole and aliphatic nitroolefin, viz., (*E*)-1-nitropent-1-ene do not go to completion even after stirring for 48 h under similar conditions. The role of water could be to increase the electrophilicity of nitroolefins through hydrogen bonding.

In conclusion, we have developed a graphite-catalyzed green methodology for the conjugate addition of indole and

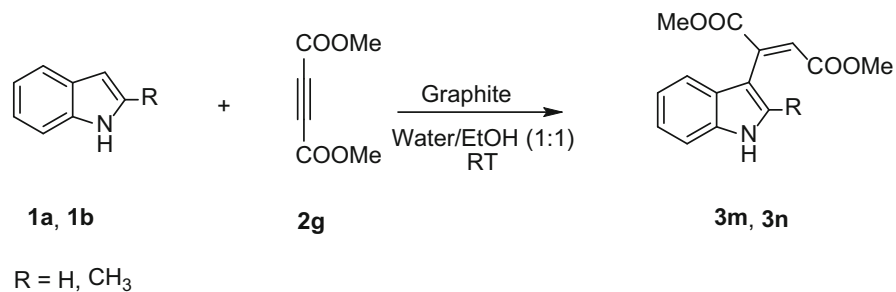
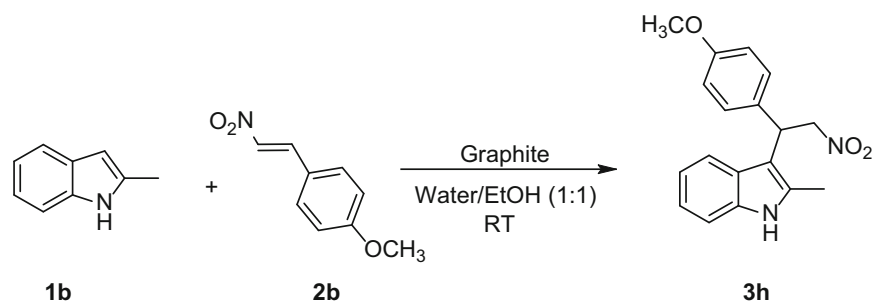
**Table 1** Michael addition of indoles catalyzed by graphite

Entry	Nucleophile 1	Electrophile 2	Product 3	Time /h	Yield /%	M.p. (lit. m.p.) /°C
<b>a</b>				7.0	61	96-98 (99 [31])
<b>b</b>				12.0	62	148-150 (150-152 [31])
<b>c</b>				10.0	57	140-142 (142 [48])
<b>d</b>				9.0	62	106-108 (107-108 [49])
<b>e</b>				8.0	60	115-117 (117-119 [25])
<b>f</b>				12.0	58	68-70 (68-69 [49])
<b>g</b>				8.0	65	90-92 (91-93 [26])
<b>h</b>				0.65	64	118-120 (120 [48])
<b>i</b>				0.85	59	118-120 (121 [48])

**Table 1** continued

Entry	Nucleophile 1	Electrophile 2	Product 3	Time /h	Yield /%	M.p. (lit. m.p.) /°C
j				0.6	66	154-156 (155-156 [33])
k				0.5	62	162-165 (-)
l				0.5	55	82-84 ([50] <sup>#</sup> )
m				0.6	80	86-88 (-)
n				0.5	90	116-118 (-)

<sup>#</sup> <sup>1</sup>H and <sup>13</sup>C NMR data are consistent

**Scheme 2****Scheme 3**

**Table 2** Recyclability of the catalyst

Cycle	Yield/%	Time/h
Native	65	1
Cycle 1	61	1
Cycle 2	59	1
Cycle 3	58	1
Cycle 4	56	1

2-methylindole to nitrostyrenes and dimethyl acetylenedicarboxylate, in water/EtOH (1:1) solvent at room temperature. The reusability of the catalyst for four cycles is also demonstrated.

## Experimental

Flash chromatography was performed on silica gel (230–400 mesh). IR spectra were recorded on Shimadzu FT-IR spectrophotometer (KBr pellet).  $^1\text{H}$  NMR (300 or 400 MHz) and  $^{13}\text{C}$  NMR (75 or 100 MHz) were recorded on Brukers instrument in  $\text{CDCl}_3$  as solvent. Chemical shifts (ppm) are relative to the internal standard  $\text{Me}_4\text{Si}$  (0 ppm). Coupling constants are reported in Hertz. High-resolution mass spectrum (HRMS) was recorded on a Micro Mass ESQTOF Mass spectrometer at IISc, Bangalore. Graphite surface area ( $116.635\text{ m}^2/\text{g}$ ) was recorded using Quantachrome, autosorb iq, ASIQC0100-4.

### General procedure

A mixture of 0.117 g indole or 0.131 g 2-methylindole (1 mmol) and 0.1639 g nitrostyrene **2a** (1.1 mmol) was stirred in presence of 0.05 g graphite (18 wt%) at room temperature in  $6\text{ cm}^3$  water/EtOH (1:1) mixture until completion of the reaction (monitored by TLC for consumption of nitrostyrene). The reaction mixture was diluted with  $10\text{ cm}^3$  water and extracted with diethyl ether ( $2 \times 10\text{ cm}^3$ ). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give a residue which was purified by flash chromatography (silica gel, hexanes/EtOAc 9:1) to afford pure products **3a–3n**. Analytical data for compounds **3a–3j** and **3l** were identical to those described in literature [25, 26, 31, 33, 48–50].

#### 2-Methyl-3-[2-nitro-1-(2-nitrophenyl)ethyl]-1H-indole

(**3k**,  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$ )

Yellow solid; m.p.: 162–165 °C;  $R_f = 0.7$  (hexanes/AcOEt 7:3); IR (KBr):  $\nu = 3,387, 1,550, 1,369\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.38$  (s, 3H), 5.10 (q,  $J = 8.8\text{ Hz}$ , 1H), 5.23 (q,  $J = 7.2\text{ Hz}$ , 1H), 5.92 (t,  $J = 8.4\text{ Hz}$ , 1H),

6.99–7.79 (m, 8H), 7.90 (br.s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.9, 36.1, 106.9, 110.9, 117.9, 120.0, 121.5, 125.3, 126.7, 128.3, 128.5, 132.7, 133.9, 134.0, 135.4, 149.7\text{ ppm}$ ; MS (EI):  $m/z = 348$  ( $[\text{M} + \text{Na}]^+$ ); HRMS (ESI): calcd. for  $\text{C}_{17}\text{H}_{15}\text{N}_3\text{NaO}_4$  ( $[\text{M} + \text{Na}]^+$ ) 348.3085, found 348.0960.

#### Dimethyl (2E)-2-(1H-indol-3-yl)but-2-enedioate

(**3m**,  $\text{C}_{14}\text{H}_{13}\text{NO}_4$ )

Yellow solid; m.p.: 86–88 °C;  $R_f = 0.6$  (hexanes/AcOEt 7:3); IR (KBr):  $\nu = 3,388, 1,732, 1,714\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.64$  (s, 3H), 3.86 (s, 3H), 6.95 (s, 1H), 7.12–7.23 (m, 2H), 7.35 (d,  $J = 8.1\text{ Hz}$ , 2H), 7.56 (d,  $J = 2.7\text{ Hz}$ , 1H), 8.50 (br.s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 51.8, 52.8, 108.8, 111.6, 119.4, 120.4, 122.3, 124.7, 126.3, 127.6, 135.6, 137.8, 166.5, 167.9\text{ ppm}$ ; MS (EI):  $m/z = 282$  ( $[\text{M} + \text{Na}]^+$ ); HRMS (ESI): calcd. for  $\text{C}_{14}\text{H}_{13}\text{NNaO}_4$  ( $[\text{M} + \text{Na}]^+$ ) 282.2471, found 282.0742.

#### Dimethyl (2E)-2-(2-methyl-1H-indol-3-yl)but-2-enedioate

(**3n**,  $\text{C}_{15}\text{H}_{15}\text{NO}_4$ )

Yellow solid; m.p.: 116–118 °C;  $R_f = 0.5$  (hexanes/AcOEt 7:3); IR (KBr):  $\nu = 3,371, 1,720\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.12$  (s, 3H), 3.61 (s, 3H), 3.78 (s, 3H), 7.02–7.25 (m, 5H), 8.24 (br.s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 12.7, 51.8, 52.8, 106.6, 110.7, 118.5, 120.0, 121.4, 127.4, 127.8, 135.1, 135.6, 138.5, 165.9, 167.9\text{ ppm}$ ; MS (EI):  $m/z = 296$  ( $[\text{M} + \text{Na}]^+$ ); HRMS (ESI): calcd. for  $\text{C}_{15}\text{H}_{15}\text{NNaO}_4$  ( $[\text{M} + \text{Na}]^+$ ) 296.2737, found 296.0899.

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## References

- Moore RE, Cheuk C, Yang XQ, Patterson GML, Bonjouklian R, Smika TA, Mynderse J, Foster RS, Jones ND, Skirtzenderuber JK, Deeter JB (1987) *J Org Chem* 52:1036
- Garnick RL, Lavery SB, LeQuesne UP (1978) *J Org Chem* 43:1226
- Moore RE, Cheuk C, Patterson GML (1984) *J Am Chem Soc* 106:6456
- Finaru A, Berthault A, Besson T, Guillaumet G, Berteina-Raboin S (2002) *Tetrahedron Lett* 43:787
- Paulvannan K, Hale R, Mesis R, Chen T (2002) *Tetrahedron Lett* 43:203
- Jand KS, Barrett V, Brockwell M, Cambridge D, Farrant DR, Foster C, Giles H, Glen RC, Hill AP, Hobbs H, Honey A, Martin GR, Salmon J, Smith D, Woollard P, Selwood DL (2001) *J Med Chem* 44:681
- Chakrabarty M, Basak R, Ghosh N, Harigaya Y (2004) *Tetrahedron* 60:1941
- Bandini M, Melchiorre P, Melloni A, Umani-Ronchi A (2002) *Synthesis* 34:1110

9. Harrington PE, Kerr MA (1996) *Synlett* 7:1047
10. Yadav JS, Abraham S, Reddy BVS, Sabitha G (2001) *Synthesis* 33:2165
11. Komoto I, Kobayashi S (2002) *Org Lett* 4:1115
12. Dessole G, Herrera RP, Ricci A (2004) *Synlett* 15:2374
13. Zhan Z-P, Yang R-F, Lang K (2005) *Tetrahedron Lett* 46:3859
14. Firouzabadi H, Iranpoor N, Nowrouzi F (2005) *Chem Commun* 789
15. Bartoli G, Bosco M, Giuli S, Giuliani A, Lucarelli L, Marcantoni E, Sambri L, Torregiani E (2005) *J Org Chem* 70:1941
16. Bartoli G, Di Antonio G, Giuli S, Marcantoni E, Marcolini M, Paoletti M (2007) *Synthesis* 39:320
17. Lin C, Hsu J, Sastry MNV, Fang H, Tu Z, Liu J-T, Ching-Fa Y (2005) *Tetrahedron* 61:11751
18. Herrera RP, Sgarzani V, Bernardi L, Ricci A (2005) *Angew Chem Int Ed* 44:6576
19. Azizi N, Arynasab F, Saidi MR (2006) *Org Biomol Chem* 4:4275
20. Jia Y-X, Zhu S-F, Yang Y, Zhou Q-L (2006) *J Org Chem* 71:75
21. Ballini R, Clemente RR, Palmieri A, Petrini M (2006) *Adv Synth Catal* 348:191
22. Sri Hari G, Nagaraju M, Marthanda Murthy M (2008) *Synth Commun* 38:100
23. An L-T, Zou J-P, Zhang L-L, Zhang Y (2007) *Tetrahedron Lett* 48:4297
24. Wu P, Wan Y, Cai J (2008) *Synlett* 19:1193
25. Kuo C-W, Wang C-C, Fang H-L, Rama Raju B, Kavala V, Habib PM, Yao C-F (2009) *Molecules* 14:3952
26. Damodiran M, Senthil Kumar R, Sivakumar PM, Doble M, Perumal PT (2009) *J Chem Sci* 121:65
27. Tran NT, Wilson SO, Franz AK (2012) *Org Lett* 14:186
28. Habib PM, Kavala V, Kuo C-W, Yao C-F (2008) *Tetrahedron Lett* 49:7005
29. Liang L, Liu Q, Zhang J, Wang F, Yuan Y (2013) *Res Chem Intermed* 39:1957
30. Jeganathan M, Kanagaraj K, Dhakshinamoorthy A, Pitchumani K (2014) *Tetrahedron Lett* 55:2061
31. Kusurkar RS, Alkobati NAH, Gokule AS, Chaudhari PM, Wagchhaure PB (2006) *Synth Commun* 36:1075
32. Kusurkar RS, Alkobati NAH, Gokule AS, Puranik VG (2008) *Tetrahedron* 64:1654
33. De Rosa M, Soriente A (2010) *Tetrahedron* 66:2981
34. Zhuang W, Hazell RG, Jorgensen KA (2005) *Org Biomol Chem* 3:2566
35. Bandini M, Garelli A, Rovinetti M, Tommasi S, Umani-Ronchi A (2005) *Chirality* 17:522
36. Kumar AV, Rao KR (2011) *Tetrahedron Lett* 52:5188
37. Sereda GA, Rajpara VB (2007) *J Chem Educ* 84:692
38. Nagai M, Yoda T, Omi S, Kodomari M (2001) *J Catal* 1:105
39. Kodomari M, Suzuli Y, Yoshida K (1997) *Chem Commun* 1567
40. Suzuki Y, Matsushima M, Kodomari M (1998) *Chem Lett* 27:319
41. Sharghi H, Sarvari MH (2003) *Synthesis* 35:243
42. Austin MJ, Groenewald T, Spiro M (1980) *J Chem Soc, Dalton Trans* 6:854
43. Yang FH, Yang RT (2003) *Carbon* 41:2149
44. Lalancette JM, Roussel R (1976) *Can J Chem* 54:2110
45. Dhumaskar KL, Tilve SG (2012) *Green Chem Lett Rev* 5:353
46. Kadam HK, Khan S, Kunkalkar RA, Tilve SG (2013) *Tetrahedron Lett* 54:1003
47. Acocella MR, Mauro M, Falivene L, Cavallo L, Guerra G (2014) *ACS Catal* 4:492
48. Meshram HM, Kumar DA, Reddy BC (2009) *Helv Chim Acta* 92:1002
49. Xie J, Zhu X, Huang M, Meng F, Wang M, Wan Y (2010) *Synth Commun* 40:3259
50. Huang G, Sun H, Qiu X, Shen Y, Jiang J, Wang L (2011) *J Organomet Chem* 696:2949