

transacylation to the more sterically favorable primary position of 1 by mild treatment at pH 8.5 in the presence of 50 mM TAPS buffer. Semisynthetic 1 exhibits identical physical properties as the natural product lysofungin including TLC, HPLC, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and MS(EI). However, the four possible diastereomers of lysofungin would be expected to exhibit very similar physical properties, so the absolute configuration of lysofungin remains ambiguous.

As shown in Figure 2, semisynthetic 1 exhibits fungicidal activity vs *Saccharomyces cerevisiae* with similar potency as is observed for natural lysofungin. At 0 min, stationary-phase cells were treated with the indicated amounts of natural lysofungin, synthetic lysofungin, or untreated. After 30 min exposure to either compound, no colony-forming units were observed at the indicated concentrations.

Now that synthetic lysofungin is available, more extensive studies can be carried out to determine its antifungal potential and the role of similar compounds in the cell.

Experimental Section

Phosphatidyl Inositol 2 to 3. A 4-mL aqueous suspension was prepared consisting of deoxycholate (12 mg, 0.03 mmol), bovine serum albumin (18 mg), CaSO_4 (5 mM), and pH 6.5 borate buffer (100 mM). This suspension was added with sonication and stirring to a dried sample of soybean phosphatidyl inositol 2 (40 mg, .049mmol). *Rhizopus arrhizus* lipase (one million units, Sigma) was then added, and the reaction was stirred at room temperature. After 2 h the reaction was quenched by the addition of 4 mL of 50% MeOH. The resulting solution was loaded onto an open RPC-18 column (5 mL of Baker octadecyl, 40 micron) and eluted with a stepwise MeOH/water gradient. The desired crude 3 (25 mg) eluted in the 70–75% MeOH fractions.

3 to Lysofungin 1. Crude 3 was dissolved in 2.5 mL of 50 mM TAPS buffer (pH 8.5) with stirring at room temperature. The reaction was monitored by HPLC (Dupont Zorbax 25-cm column, UV absorbance at 205 nm, 67% 10 mM potassium phosphate (pH 6.5) 33% acetonitrile, 1 mL/min, retention times 11.2 min for 3 and 14.2 min for 1). After 18 h the reaction was applied to an open RPC-18 column (5 mL of Baker octadecyl, 40 μm) and eluted with a MeOH/water gradient. The desired 1 (15 mg) eluted with 80% MeOH and upon lyophilization from water was obtained as a white solid.

$^1\text{H-NMR}$ (CD_3OD): 0.92 (t, $J = 6$ Hz, 3 H), 1.28–1.42 (m, 14 H), 1.56–1.68 (m, 2 H), 2.07 (dd, $J = 7$ and 6 Hz, 4 H), 2.45 (t, $J = 8$ Hz, 2 H), 2.78 (t, $J = 6$ Hz, 2 H), 3.20 (t, $J = 9$ Hz, 2 H), 3.38 (dd, $J = 3$ and 8 Hz, 1 H), 3.63 (t, $J = 10$ Hz, 1 H), 3.77 (t, $J = 9$ Hz, 1 H), 3.92 (ddd, $J = 3, 7,$ and 10 Hz, 1 H), 3.98 (dd, $J = 2$ and 7 Hz, 2 H), 4.06–4.12 (m, 1 H), 4.15 (dd, $J = 4$ and 8 Hz, 1 H), 4.21 (t, $J = 3$ Hz, 1 H), 5.3–5.4 (m, 4 H).

$^{13}\text{C-NMR}$ (CD_3OD): 14.4, 23.6, 26.0, 26.5, 28.2 (2 \times), 30.2 (2 \times), 30.3, 30.5, 30.7, 32.7, 34.9, 66.3, 67.8 (d, $J = 5.8$ Hz), 70.0 (d, $J = 7.7$ Hz), 72.9, 73.1, (d, $J = 1.9$ Hz), 73.3 (d, $J = 5.5$ Hz), 74.1, 76.3, 78.4 (d, $J = 6.1$ Hz), 129.1, 129.1, 130.9, 130.9, 175.4.

FAB-MS (negative ion) indicated a MW of 596 (observed (M – H) at m/z 595).

Fungicidal Biology. *Saccharomyces cerevisiae* MY1117, a presumed wild-type, diploid strain of unknown genotype was obtained from the Merck culture collection and maintained on YEPD (1% yeast extract, 2% peptone, 2% glucose, and 1.5% agar) slants at 40 $^\circ\text{C}$. To determine the effects of lysofungin on cell viability, cultures in early stationary phase were diluted to approximately 1×10^5 cells/mL in sterile saline, aliquoted into tubes containing the appropriate drug, and incubated at 30 $^\circ\text{C}$. Samples were removed periodically, diluted in sterile saline, and plated on SDA (Sabouraud's Dextrose Agar, Difco). Colonies were enumerated after 36–48 h of incubation at 30 $^\circ\text{C}$. The limit of detection of the assay was 20 CFU/mL.

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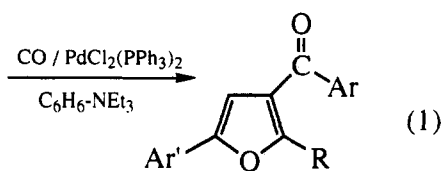
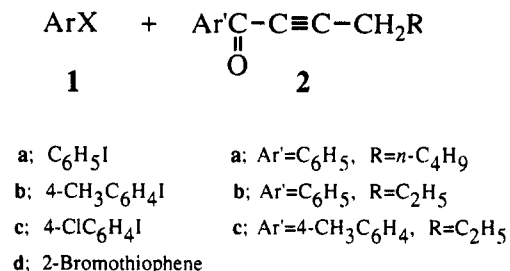
Palladium-Catalyzed Cross-Carbonylation of Aryl Iodides and 1-Aryl-2-alkyn-1-ones

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Palladium-catalyzed carbonylation of aryl halides is a useful tool for the preparation of a variety of aromatic carbonyl compounds; the reaction of intermediary aryl-palladium complexes with various nucleophiles and organometallic reagents gives the products.¹ While effective methods for cyclo-carbonylation reactions of haloalkenes including 2-alkenyl-1-iodobenzenes² and allyl acetates³ to give cyclic ketones have also been developed, intermolecular cross-carbonylation of aryl halides with alkenes and alkynes using palladium catalysts are less common.⁴ We report herein our findings that cross-carbonylation of aryl iodides (1a–c) or bromothiophene (1d) and 1-aryl-2-alkyn-1-ones (2a–c) proceeds efficiently in the presence of dichlorobis(triphenylphosphine)palladium ($\text{PdCl}_2(\text{PPh}_3)_2$) using triethylamine as base to give 2-alkyl-3-aryl-5-arylfurans (3–8) in good yield (eq 1 and Table I).⁵



3: $\text{Ar}=\text{C}_6\text{H}_5$, $\text{Ar}'=\text{C}_6\text{H}_5$, $\text{R}=\text{n-C}_4\text{H}_9$

4: $\text{Ar}=\text{C}_6\text{H}_5$, $\text{Ar}'=\text{C}_6\text{H}_5$, $\text{R}=\text{C}_2\text{H}_5$

5: $\text{Ar}=\text{C}_6\text{H}_5$, $\text{Ar}'=4\text{-CH}_3\text{C}_6\text{H}_4$, $\text{R}=\text{C}_2\text{H}_5$

6: $\text{Ar}=4\text{-CH}_3\text{C}_6\text{H}_4$, $\text{Ar}'=\text{C}_6\text{H}_5$, $\text{R}=\text{n-C}_4\text{H}_9$

7: $\text{Ar}=4\text{-ClC}_6\text{H}_4$, $\text{Ar}'=\text{C}_6\text{H}_5$, $\text{R}=\text{n-C}_4\text{H}_9$

8: $\text{Ar}=2\text{-thienyl}$, $\text{Ar}'=\text{C}_6\text{H}_5$, $\text{R}=\text{C}_2\text{H}_5$

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(5) The relevant palladium-catalyzed carbonylation reactions of aryl halides with terminal alkynes, 2-methyl-3-butyn-2-ol⁶ and 3-aryl-1-propynes,⁷ to give 3(2H)-furanones and 3-arylidenebutenolides, respectively, have been recently reported. The initial step in these reactions is considered to involve generation of the corresponding 1-aryl-2-propyn-1-ones.⁸

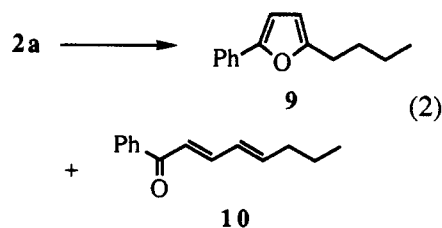
Table I. Palladium-Catalyzed Cross-Carbonylation of Aryl Halides 1 and 1-Aryl-2-alkyn-1-ones 2^a

| run | halide | alkynone | product | % yield ^b |
|----------------|--------|----------|---------|----------------------|
| 1 ^c | 1a | 2a | 3 | 65 (71) |
| 2 | 1a | 2a | 3 | 66 |
| 3 ^d | 1a | 2a | 3 | (36) |
| 4 | 1a | 2b | 4 | 66 |
| 5 ^c | 1a | 2c | 5 | 73 |
| 6 | 1b | 2a | 6 | 68 |
| 7 | 1c | 2a | 7 | 70 |
| 8 ^e | 1d | 2b | 8 | 75 |

^a Reaction conditions: 1 (2.5 mmol), 2 (2.0 mmol), PdCl₂(PPh₃)₂ (0.02 mmol), CO (15 atm, 213 psi), 120 °C, 18 h, C₆H₆ (2.5 mL)-NEt₃ (2.5 mL). ^b Based on 2 charged. Value in parentheses is GLC yield. ^c In NEt₃ (5.0 mL). ^d In C₆H₆ (5.0 mL)-NEt₃ (0.7 mL). ^e PdCl₂(PPh₃)₂ (0.06 mmol).

Treatment of iodobenzene (1a) (2.5 mmol) with 1-phenyl-2-octyn-1-one (2a) (2.0 mmol) in triethylamine (5 mL) in the presence of PdCl₂(PPh₃)₂ (0.02 mmol) under carbon monoxide (15 atm, 213 psi at room temperature) at 120 °C for 18 h gave 3-benzoyl-2-butyl-5-phenylfuran (3) in a yield of 65% based on 2a charged. The structure of 3 was determined on the basis of its ¹H and ¹³C NMR spectra⁹ and a transformation reaction with hydrazine (vide infra). The reaction could also be carried out in benzene (2.5 mL)-triethylamine (2.5 mL), but the yield of 3 was considerably decreased in benzene (5 mL)-triethylamine (0.7 mL, 5 mmol). Reactions using bromobenzene and 2-methyl-4-decyn-3-one in place of the substrates 1 and 2, respectively, did not produce the cyclized products.

It has been reported that 2-alkyn-1-ones are transformed into either 2,5-disubstituted furans¹⁰ or 2,4-alkadien-1-ones¹¹ under the influence of palladium catalysts.^{12,13} Treatment of the alkynone 2a under the present carbonylation conditions gave a mixture of 2-butyl-5-phenylfuran (9) (7%) and 1-phenyl-(2E,4E)-octa-2,4-dien-1-one (10) (15%) together with other unidentified products (eq 2).¹⁴ The furan 9 (25%) was also produced from 2a (55%

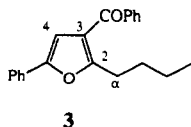


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(9) The signal for C₃ at 121.90 ppm in the ¹³C NMR spectrum without ¹H-irradiation was observed as multiplet coupled with H₄ and H_α. Selective irradiation on H_α revealed the coupling constant J_{C₃H₄} to be 3.1 Hz; the coupling between C₃ and H_α disappeared.

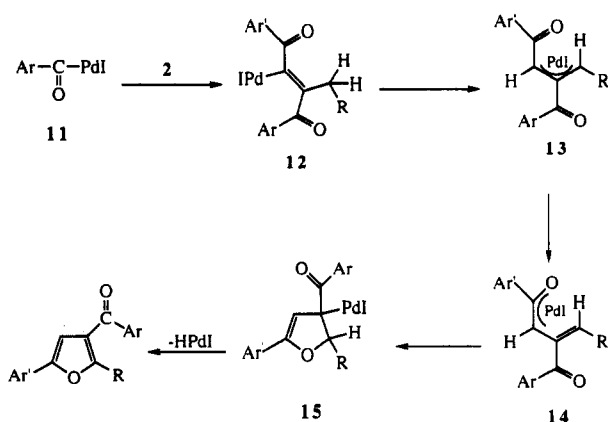


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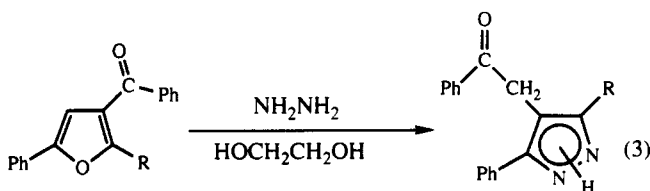
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Scheme I

conversion) as a single major product in the presence of triethylamine alone under nitrogen. It was confirmed that treatment of 1a with either 9 or 10 under the carbonylation conditions did not afford 3.¹⁵ This may indicate that the cross-carbonylation of 1a with 2a does not involve 9 and 10, although a small quantity of 9 was detected in the product mixture.

Therefore, the reaction of benzoylpalladium species 11 generated in situ with unchanged 2 to give intermediate 12 may participate in the reaction sequence as shown in Scheme I, in which neutral ligands are omitted.¹⁶ The next step would involve a 1,3-hydrogen shift to give π-allyl complex 13. Subsequently, elimination of hydridoiodopalladium accompanied by ring-closure via oxallyl species 14 affords the furans.¹⁷

It is worth noting that furan 3 was transformed into 4-(benzoylmethyl)-3-butyl-5-phenylpyrazole (16) and/or its tautomer by heating it in the presence of hydrazine in ethylene glycol in a yield of 70% (eq 3, see also Experimental Section).¹⁸ Similarly, pyrazole derivative 17 (65%) was obtained from 4.



3; R = n-Bu

4; R = Et

16; n-Bu 70%

17; Et 65%

Experimental Section

¹H and ¹³C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for CDCl₃ solutions. MS data were obtained by EI. 1-Aryl-2-alkyn-1-ones 2a-c¹⁹ and PdCl₂(PPh₃)₂¹ were

(14) The reaction of bromobenzene with 2a also gave a similar product mixture derived from 2a, bromobenzene (>80%) being recovered. This suggests that the use of reactive aryl halides is essential for the cross-carbonylation.

(15) The furan 9 was recovered almost quantitatively. The reaction of 1a with 10 gave an air-sensitive cross-carbonylation product as a single major product other than 3 whose characterization has not yet succeeded.

(16) However, the possibility that 2 is transformed into 1-aryl-2,3-alkadien-1-ones, followed by the reaction with 11 to give 13, cannot be excluded.

(17) The oxallyl species is kindly suggested by a reviewer.

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prepared by the methods reported previously. Other starting materials were commercially available and were purified by standard methods before use.

General Procedure for Cross-Carbonylation of 1 and 2. A mixture of 1 (2.5 mmol), 2 (2 mmol), and PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol) in benzene (2.5 mL)-triethylamine (2.5 mL) was added into a 50-mL stainless steel autoclave and carbon monoxide (15 atm, 213 psi at room temperature) was charged. Then, the mixture was magnetically stirred at 120 °C for 18 h. After cooling, the mixture was poured into dilute hydrochloric acid, extracted with ether, washed with water, and dried over magnesium sulfate. The product was isolated by column chromatography on silica gel using hexane-ethyl acetate as eluant.

3-Benzoyl-2-butyl-5-phenylfuran (3): oil; ¹H NMR δ 0.94 (t, 3 H, *J* = 7.3 Hz), 1.40 (qt, 2 H, *J* = 7.3, 7.3 Hz), 1.75 (tt, 2 H, *J* = 7.3, 7.3 Hz), 2.97 (t, 2 H, *J* = 7.3 Hz), 7.24-7.84 (m, 10 H); ¹³C NMR δ 13.75, 22.36, 27.70, 30.34, 106.60, 121.92, 123.70, 127.70, 128.34, 128.73, 129.00, 130.07, 132.08, 139.20, 151.44, 162.90, 191.24; MS *m/z* 304 (M⁺). Anal. Calcd for C₂₁H₂₀O₂: C, 82.15; H, 6.91. Found: C, 82.31; H, 6.61.

3-Benzoyl-2-ethyl-5-phenylfuran (4): oil; ¹H NMR δ 1.34 (t, 3 H, *J* = 7.3 Hz), 3.00 (q, 2 H, *J* = 7.3 Hz), 6.79 (s, 1 H), 6.80-7.85 (m, 10 H); ¹³C NMR δ 12.33, 21.65, 106.54, 121.50, 123.72, 127.70, 128.34, 128.44, 128.72, 128.97, 132.18, 139.21, 151.46, 163.69, 191.15; MS *m/z* 276 (M⁺). Anal. Calcd for C₁₉H₁₆O₂: C, 82.57; H, 5.85. Found: C, 82.47; H, 5.77.

3-Benzoyl-2-ethyl-5-(4-methylphenyl)furan (5): oil; ¹H NMR δ 1.34 (t, 3 H, *J* = 7.3 Hz), 2.37 (s, 3 H), 2.99 (q, 2 H, *J* = 7.3 Hz), 6.73 (s, 1 H), 7.19 (d, 2 H, *J* = 7.8 Hz), 7.46-7.57 (m, 5 H), 7.83-7.86 (m, 2 H); ¹³C NMR δ 12.38, 21.29, 21.68, 105.82, 121.48, 123.74, 127.39, 128.35, 129.00, 129.43, 132.18, 137.66, 139.30, 151.73, 163.42, 191.34; MS *m/z* 290 (M⁺). Anal. Calcd for C₂₀H₁₈O₂: C, 82.72; H, 6.26. Found: C, 82.45; H, 6.32.

2-Butyl-3-(4-methylbenzoyl)-5-phenylfuran (6): oil; ¹H NMR δ 0.93 (t, 3 H, *J* = 7.3 Hz), 1.40 (qt, 2 H, *J* = 7.3, 7.3 Hz), 1.74 (tt, 2 H, *J* = 7.3, 7.3 Hz), 2.44 (s, 3 H), 2.98 (t, 2 H, *J* = 7.3 Hz), 6.79 (s, 1 H), 7.25-7.40 (m, 5 H), 7.64-7.77 (m, 4 H); ¹³C NMR δ 13.76, 21.61, 22.38, 27.70, 30.28, 106.62, 122.11, 123.70, 127.63, 128.72, 129.03, 129.23, 130.13, 136.53, 142.95, 151.33, 162.57, 190.99; MS *m/z* 318 (M⁺). Anal. Calcd for C₂₂H₂₂O₂: C, 82.97; H, 6.98. Found: C, 82.68; H, 7.06.

2-Butyl-3-(4-chlorobenzoyl)-5-phenylfuran (7): oil; ¹H NMR δ 0.94 (t, 3 H, *J* = 7.3 Hz), 1.41 (qt, 2 H, *J* = 7.3, 7.3 Hz), 1.75 (tt, 2 H, *J* = 7.3, 7.3 Hz), 2.99 (t, 2 H, *J* = 7.3 Hz), 7.25-7.47 (m, 5 H), 7.64-7.80 (m, 4 H); ¹³C NMR δ 13.74, 22.37, 27.74, 30.21, 106.18, 121.61, 123.74, 127.82, 128.68, 128.76, 129.89, 130.42, 137.48, 138.56, 151.62, 163.14, 189.87; MS *m/z* 338 (M⁺). Anal. Calcd for C₂₁H₁₈O₂Cl: C, 74.43; H, 5.66; Cl, 10.46. Found: C, 74.20; H, 5.67; Cl, 10.60.

2-Ethyl-3-(2-thienylcarbonyl)-5-phenylfuran (8): mp 69-71 °C (from hexane); ¹H NMR δ 1.35 (t, 3 H, *J* = 7.3 Hz), 3.05 (q, 2 H, *J* = 7.3 Hz), 6.99 (s, 1 H), 7.17 (dd, 1 H, *J* = 2.9, 4.9 Hz), 7.25-7.43 (m, 3 H), 7.67-7.79 (m, 4 H); ¹³C NMR δ 12.42, 21.62, 105.75, 121.18, 123.79, 127.82, 127.90, 128.79, 130.05, 132.85, 133.30, 145.05, 151.73, 163.65, 182.10; MS *m/z* 282 (M⁺). Anal. Calcd for C₁₇H₁₄O₂S: C, 72.30; H, 5.01; S, 11.36. Found: C, 72.28; H, 4.96; S, 11.11.

Rearrangement of 2a. (a) The alkynone 2a (200 mg, 1 mmol) in triethylamine (3 mL) was heated under nitrogen in a 50-mL stainless steel autoclave at 120 °C for 18 h. After evaporation of the solvent, the product mixture was chromatographed on silica gel using hexane-ethyl acetate as eluant. The furan 9 (49 mg, 25%) was obtained from the first fraction as an oil: ¹H NMR δ 0.94 (t, 3 H, *J* = 7.3 Hz), 1.41 (qt, 2 H, *J* = 7.3 Hz), 1.67 (tt, 2 H, *J* = 7.3 Hz), 2.68 (t, 2 H, *J* = 7.3 Hz), 6.06 (d, 1 H, *J* = 3.2 Hz), 6.54 (d, 1 H, *J* = 3.2 Hz), 7.18-7.25 (m, 1 H), 7.33-7.37 (m, 2 H), 7.61-7.71 (m, 2 H); ¹³C NMR δ 13.82, 22.28, 27.87, 30.23, 105.61, 106.80, 123.31, 126.67, 128.55, 131.27, 152.07, 156.45; MS *m/z* 200 (M⁺). The second fraction contained 2a (88 mg, 45%).

(b) A mixture of 2a (400 mg, 2 mmol) and PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol) in benzene (2.5 mL)-triethylamine (2.5 mL) was heated in a 50-mL stainless steel autoclave under carbon monoxide (15 atm, 213 psi at room temperature) at 120 °C for 18 h. For-

mation of 9 (27 mg, 7%) and 10 (58 mg, 15%) was confirmed by GC and GC-MS analyses. An authentic sample of 10 was prepared by treatment of 2a (2 mmol) with RuCl₂(PPh₃)₃ (20 mg, 0.02 mmol) in refluxing acetonitrile (5 mL) for 15 h.²⁰

1-Phenyl-(2E,4E)-octa-2,4-dien-1-one (10):²¹ oil; ¹H NMR δ 0.93 (t, 3 H, *J* = 7.3 Hz), 1.48 (qt, 2 H, *J* = 7.3, 7.3 Hz), 2.21 (t, 2 H, *J* = 7.3 Hz), 6.21-6.35 (m, 2 H), 6.87 (d, 1 H, *J* = 15.1 Hz), 7.52-7.56 (m, 4 H), 7.92-7.94 (m, 2 H); ¹³C NMR δ 13.66, 21.89, 35.20, 123.56, 128.32, 128.47, 129.26, 132.46, 138.29, 145.41, 146.31, 190.91; MS *m/z* 200 (M⁺).

Reaction of the Furan 3 or 4 with Hydrazine. A mixture of 3 or 4 (1 mmol) and hydrazine hydrate (1.0 g) in ethylene glycol (2 mL) was heated at 150 °C for 2 h. After workup, the corresponding pyrazole was isolated by column chromatography on silica gel using hexane-ethyl acetate as eluant. The pyrazoles 16 and 17 may, at least in solution, exist as mixture of annular tautomers, as usual N-unsubstituted pyrazoles.²² The C₃ and C₅ carbons in their ¹³C NMR spectra showed more than two peaks (very weak), respectively. Probably, there are also aggregates.²²

4-(Benzoylmethyl)-3(5)-butyl-5(3)-phenylpyrazole (16): mp 144-146 °C (from hexane-benzene); ¹H NMR δ 0.90 (t, 3 H, *J* = 7.3 Hz), 1.36 (qt, 2 H, *J* = 7.3, 7.3 Hz), 1.62 (tt, 2 H, *J* = 7.3, 7.3 Hz), 2.57 (t, 2 H, *J* = 7.3 Hz), 4.20 (s, 2 H), 7.34-7.45 (m, 8 H), 7.54-7.57 (m, 2 H); ¹³C NMR 13.78, 22.50, 25.40, 30.81, 34.06, 107.99, 127.93, 128.00, 128.24, 128.57, 128.68, 132.22, 133.09, 136.58, 197.31, (C₃ and C₅ 128.30, 128.48, 147.66, 147.73); MS *m/z* 318 (M⁺). Anal. Calcd for C₂₁H₂₂N₂O: C, 79.20; H, 6.98; N, 8.80. Found: C, 79.62; H, 7.00; N, 8.56.

4-(Benzoylmethyl)-3(5)-ethyl-5(3)-phenylpyrazole (17): mp 119-120 °C (from hexane-benzene); ¹H NMR δ 1.25 (t, 3 H, *J* = 7.3 Hz), 2.60 (q, 2 H, *J* = 7.3 Hz), 4.20 (s, 2 H), 7.34-7.45 (m, 8 H), 7.54-7.56 (m, 1 H), 7.92-7.94 (m, 2 H); ¹³C NMR δ 13.02, 18.93, 34.03, 107.60, 127.95, 128.00, 128.24, 128.55, 128.64, 132.27, 133.08, 136.53, 197.35, (C₃ and C₅ 128.12, 128.15, 128.33, 128.41, 147.69, 147.72, 148.72); MS *m/z* 290 (M⁺). Anal. Calcd for C₁₉H₁₈N₂O: C, 78.58; H, 6.26; N, 9.65. Found: C, 78.20; H, 6.19; N, 9.55.

Registry No. 1a, 591-50-4; 1b, 624-31-7; 1c, 637-87-6; 1d, 1003-09-4; 2a, 27259-10-5; 2b, 65236-43-3; 2c, 108462-79-9; 3, 142395-76-4; 4, 142395-77-5; 5, 142395-78-6; 6, 142395-79-7; 7, 142395-80-0; 8, 142395-81-1; 9, 80866-26-8; 10, 96412-99-6; 16, 142395-82-2; 17, 142395-83-3; PdCl₂(PPh₃)₂, 13965-03-2.

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Specificity of Antibody-Catalyzed Transesterifications Using Enol Esters: A Comparison with Lipase Reactions

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The rapidly growing field of catalytic antibodies has become an effective approach to catalyst design.¹ Since the active site of a catalytic antibody is induced by the designed hapten, the substrate specificity and stereoselectivity of antibody catalysis are therefore expected to be

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