Tetrahedron Vol. 44, No 15, pp 4967 to 4972, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

RHODIUM (1) CATALYSED REGIOSPECIFIC CYCLISATION OF 1,6-ENYNES TO METHYLENECYCLOHEX-2-ENES

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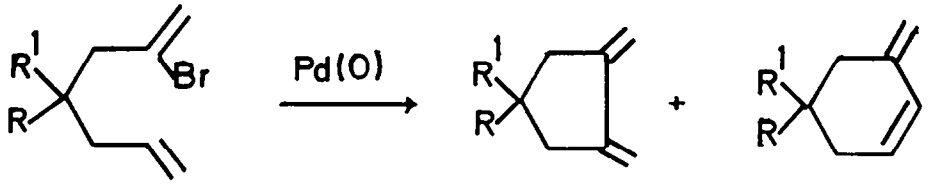
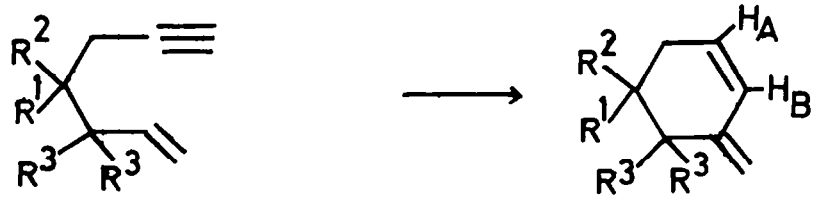
(*Received in UK* 24 *May* 1988)

Abstract. 1,6-Enynes are cyclised regiospecifically by 5 mol % of Wilkinson's catalyst [$(Ph_3P)_3RhCl$] in acetonitrile at 80°C to give the corresponding methylene cyclohex-2-enes usually in good yield (62-83%). Terminal substitution on either the alkene or alkyne moieties effectively suppresses the reaction. 4-Benzoylaza- and 4-benzylaza-hepta-1,6-enynes are similarly cyclised to 5-methylene-1,2,5,6-tetrahydropyridines in 20-28% yield. The mechanism of cyclisation is discussed and is shown to involve a 6-exo-trig process.

The utilisation of transition metal complexes for the catalytic cyclisation of dienes[1,2], enynes[3,4] and diynes[5] is providing important new methodology for the construction of carbo- and hetero-cyclic compounds. Rhodium[1,5], palladium and nickel[4] complexes are proving especially valuable catalysts. The cyclisation of 1,6-dienes and 1,6-enynes is usually regiospecific for formation of the 5-membered ring product. However, our recent work on intramolecular Heck reactions, e.g. (1)⟶(2)+(3) shows that although the 5-exo-trig cyclisation product (2) is kinetically favoured, the 6-endo-trig product (3) can be the major product with certain substrates and catalysts.[6]



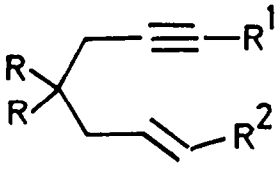
(1) (2) (3)



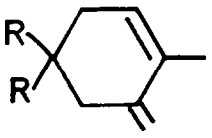
(4) a. $R^1=R^2=CO_2Et$, $R^3=H$
b. $R^1=R^2=COMe$, $R^3=H$
c. $R^1=H, R^2=CO_2Me, R^3=Me$
d. $R^1=R^2=SO_2Ph$, $R^3=H$

(5) a. $R^1=R^2=CO_2Et$, $R^3=H$
b. $R^1=R^2=COMe$, $R^3=H$
c. $R^1=H, R^2=CO_2Me, R^3=Me$
d. $R^1=R^2=SO_2Ph$, $R^3=H$

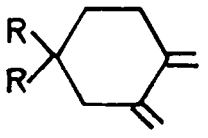
We now report the rhodium (1) catalysed regiospecific cyclisation of 1,6-enynes to methylenecyclohex-2-enes. Thus (4a) cyclises to (5a) (73%) on heating (24h) at 80°C in acetonitrile in the presence of 5 mol % of Wilkinson's catalyst [$(Ph_3P)_3RhCl$]. Under analogous conditions (4b) cyclises to (5b) (62%) over 23h. The cyclisation of (4c) to (5c) (MeCN, 80°C, 6h), occurs in 83% yield. The more rapid rate of cyclisation in the latter case is presumably due to the operation of the Thorpe-Ingold effect.[7] In contrast (4d) did not cyclise to (5d) under the same conditions but instead gave a low yield (20%) of (2, $R=R^1 = SO_2Ph$). Trost has reported that (4d) is cyclised to (2, $R=R^1=SO_2Ph$) by a palladium catalyst in an undisclosed yield.[2] Terminal substitution on the alkene (6a) effectively suppressed the cyclisation reaction and only trace amounts ($\lesssim 5\%$) of a mixture of (7) and (8) was detected, whilst terminal substitution on the alkyne moiety (6b) totally suppressed the cyclisation.



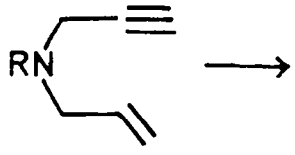
(6) a. $R=CO_2Et$, $R^1=H$, $R^2=Me$
b. $R^1=Me$, $R^2=H$, $R=CO_2Et$



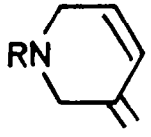
(7) $R=CO_2Et$



(8) $R=CO_2Et$

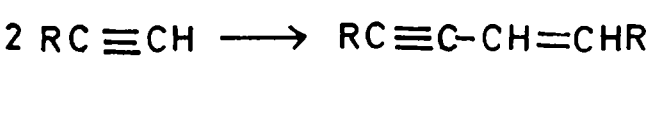


(9) a. R=COPh
b. $R=CH_2Ph$

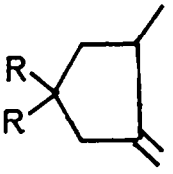


(10) a. R=COPh
b. $R=CH_2Ph$

(11)



(12) (13)



(14) $R=CO_2Et$

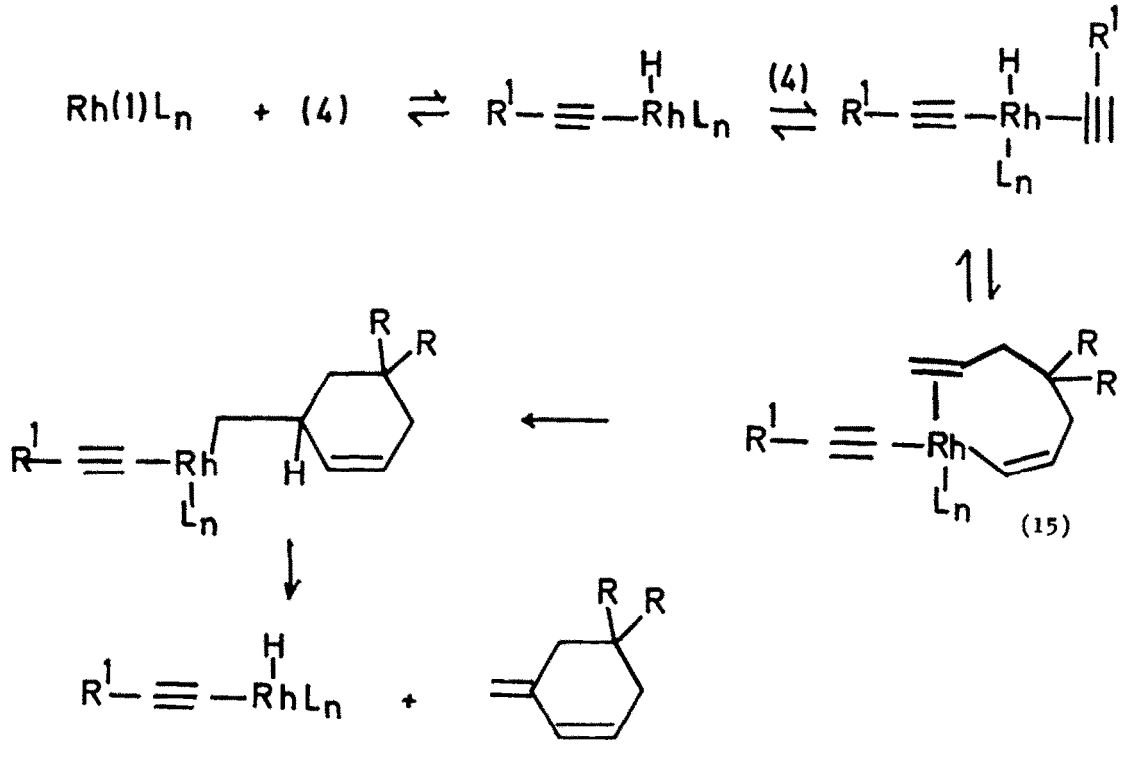
The amide (9a) cyclises (MeCN, 80°C, 0.5h) to (10a) in 20% yield using 5 mol% $(PPh_3)_3RhCl$ whilst (9b) cyclises (MeCN, 80°C, 24h) to (10b) more slowly even when 10 mol% $(PPh_3)RhCl_3$ is employed and gives an equally disappointing yield (28%). Good yields of 5-membered pyrrolidines corresponding to (2) have been reported by Trost for palladium catalysed cyclisations.[8] The enynes (11, X = S, SO, SO_2 or O) all fail to cyclise in acetonitrile at 80°C using Wilkinson's catalyst. The starting material is either recovered unchanged or is polymerised.

In comparison we observe that (4a) is cyclised (MeCN, 80°C, 1h) to (2, $R=R^1=CO_2Et$) (78%) by a catalyst comprising 5 mol% palladium acetate and 10 mol% triphenylphosphine. An analogous reaction of (4a) with the addition of 10 mol% piperidinium formate as a hydride ion source gives (2, $R=R^1=CO_2Et$) (38%) together with (14) (8.5%).[1]

Mechanism. A plausible mechanism for the reaction is shown in the Scheme. The possible occurrence of free (2) as an intermediate in the reaction was ruled out when no (5a) was detected on subjecting (2, R=R^1=CO_2Et) to the standard reaction conditions.

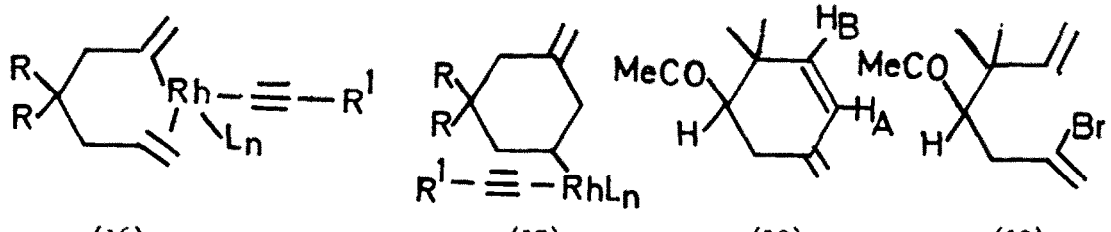
Insertion of Rh(1) into the C-H of terminal alkynes is a well known process that usually leads to enynes via regiospecific direct coupling, i.e. (12)⟶(13). In the present case the insertion of the alkyne into the rhodium-hydride bond accompanied by coordination of the alkene moiety of (4) to rhodium (14) permits insertion of the coordinated alkene into the vinyl-rhodium bond. This process is more facile than reductive elimination of rhodium (1) from (15) with accompanying vinyl-alkyne coupling. The latter process predominates when the terminal alkene is substituted by alkyl groups.[10] The key intermediate (15) (Scheme) cyclises by a 6-exo-trig process. Elimination of a rhodium hydride species then regenerates the active catalyst.

A possible alternative intermediate is (16) which would also furnish a methylenecyclohex-2-ene via 6-endo-trig cyclisation to (17) and subsequent elimination of a rhodium hydride species. This alternative mechanism is ruled out by the observation that the cyclisation of (4c) gives (5c) and not (18). In particular the p.m.r. signal (250MHz) for H_A in (5c) occurs as a broad doublet



R^1 = $CH_2CR_2CH_2CH{=}CH_2$

SCHEME



(16) (17) (18) (19)

at δ 5.72 due to coupling to both H_B and the adjacent methylene group, whilst H_A and H_B in (17) give rise to an AB pattern centred at δ 6.01 and 5.50. The methylenecyclohex-2-ene (17) has been previously prepared by us from (18) via an intramolecular Heck reaction.[6]

The mechanism in the Scheme accords with the usual regiochemistry of the addition of rhodium hydride species to alkynes[9,10] and with our observations that 5-exo-trig cyclisations are more facile than 6-endo-trig cyclisations, whilst 6-exo-trig cyclisations are more facile than 7-endo-trig cyclisations.[6] There is a further interesting mechanistic feature inherent in the proposed Scheme. The addition of rhodium hydride species to alkynes is known to occur with cis-stereochemistry.[11] However the key intermediate (15) in the Scheme is formally the product of a trans-addition. Thus stereomutation of an initial cis-vinylrhodium species must precede formation of (15). Palladium hydride species add to terminal alkynes with opposite regiochemistry to rhodium hydrides and this has been developed as a route to substituted 1,3-enynes.[12]

Experimental. General experimental details were as previously noted.[1] Petroleum ether refers to the fraction with b.p. 40-60°C. Infrared spectra were determined for thin films unless otherwise stated. 1,6-Enynes were prepared by literature methods except as noted below.

1,6-Fnynes

Methyl 3,3-dimethylhepta-1-ene-6-yne-4-carboxylate (4c). Methyl 3,3-dimethylpent-4-enoate (5.0g, 3.5mmol), was added to a solution of lithium diisopropylamide [from 1.6M n-butyllithium (25ml, 4.0mmol)] in tetrahydrofuran (50ml) at -63°C. After 15 min. HMPA (5ml) was added and the mixture stirred for a further 15 min. at -63°C when propargyl bromide (4.2g, 3.5mmol) was added maintaining the temperature at -63°C for a further 20 min. The reaction mixture was then allowed to warm to room temperature, the solvent removed under reduced pressure and the residue partitioned between ether and water. The dried ($MgSO_4$) ether solution was evaporated and the residual oil distilled to afford the product (5.2g, 82%) as a colourless oil, b.p. 60-64°C/2.5 mmHg (Found: C, 71.00; H, 9.10. $C_{11}H_{16}O_2$ requires C, 71.40; H, 9.60%); δ 5.81 (q, 1H, CH=CH_2), 5.0 (m, 2H, CH=CH_2), 3.72 (s, 3H, OMe), 2.5 (m, 2H, CH_2C), 2.27 (m, 1H, $CHCO_2Me$), 1.94 (t, 1H, C CH), and 1.06 and 1.05 (2 x s, 2 x 3H, Me); ν_{max}. 3083, 2966, 1735 and 1630 cm^{-1}; m/z(%) 179 (M-1,2), 121(55), 120(10), 112(11), 111(10), 109(8), 105(19), 79(10), 77(10), 70(12) and 69(100).

Diethyl octa-1-ene-7-yne-5,5-dicarboxylate (6a). Diethyl but-2-enylmalonate (10.7g, 5mmol) was added over 5 min. to a solution of sodium ethoxide [from sodium (1.2g, 5.2mmol)] in ethanol (150ml) under a nitrogen atmosphere. The mixture was stirred for 15 min. and then propargyl bromide (6.21g, 5.2mmol) was added over 5 min. and the resulting mixture stirred at room temperature overnight. The reaction was worked up as described above. The product (7.6g, 60%) distilled as colourless oil, b.p. 89-94°C/0.75mmHg (Found: C, 66.55; H, 8.15. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.00%); δ 5.60 and 5.20 (2 x m, 2 x 1H, CH=CH), 4.20 (q, 2 x 2H, OCH_2Me), 2.78 (d, 2H, CH_2C), 2.73 (d, 2H, CH_2CH=), 2.01 (t, 1H, C CH), 1.66 (m, 3H, CH=CHMe), and 1.25 (t, 2 x 3H, OCH_2Me); ν_{max} 3285, 2981, 2939 and 1735 cm^{-1}; m/z(%) 252 (M^+,0.5), 223(5), 213(61), 207(9), 179(22), 178(57), 168(11), 167(100), 161(12), 151(21), 133(13), 121(38), 105(48), 95(16), 91(17), 79(17) and 77(14).

Diethyl octa-1-ene-6-yne-4,4-dicarboxylate (6b).

Prepared from diethyl allylmalonate (3.0g, 1.5mmol), 1-bromobut-2-yne (2.5g, 1.88mmol) and sodium ethoxide [from sodium (0.35g, 1.52mmol)] in ethanol (20ml) in an analogous manner to that described above. The product (2.3g, 61%) distilled as a colourless oil, b.p. 60-63°C/0.5mmHg (Found: C, 67.00; H, 8.20. $C_{14}H_{20}O_4$ requires C, 66.65; H, 8.00%); δ 5.6 (m, 1H, CH=CH_2), 5.1 (m, 2H, CH=CH_2), 4.2 (q, 2 x 2H, OCH_2Me), 2.78 (br s, 2H, CH_2C), 2.73 (d, 2H, CH_2CH=), 1.8 (br s, 3H, CMe), and 1.26 (t, 2 x 3H, OCH_2Me); ν_{max} 3210, 2978, 2849 and 1730 cm^{-1}; m/z(%) 252 (M^+,1), 251(5), 223(4), 213(60), 179(20), 178(60), 168(22), 167(100), 151(20), 121(41), and 105(45).

General Procedure for Rh(I) Catalysed Cyclisation Reactions. Wilkinson's catalyst [$(PPh_3)_3RhCl$] (5 or 10 mol %) was added to a solution of the 1,6-enyne in dry acetonitrile. The resulting mixture was stirred and boiled under reflux under a nitrogen atmosphere monitored by g.l.c. (2.5% SGR, 2m). After the reaction was complete the solvent was removed under reduced pressure and the residue filtered through a short column of neutral alumina eluting with 3:1 v/v petroleum ether-ether to remove the catalyst.

4,4-Di(phenylsulphonyl)-1,2-bis(methylene)cyclopentene (2, R=R^1=SO_2Ph). Prepared from 4,4-di(phenylsulphonyl)hepta-1-ene-6-yne (500mg), with a 3h reaction time, by the general method. Work up followed by preparative t.l.c. afforded the product (100mg, 20%) as a pale yellow solid, m.p. 63-66°C. Accurate mass: 374.0654 $C_{19}H_{18}O_4S_2$ requires 374.0646; δ 7.8 (m, 10H, ArH), 5.27 and 4.82 (2 x br s, 2 x 2H, C=CH_2), and 3.40 (br s, 4H, CH_2=CH_2); ν_{max}(KBr) 3424, 2921, 1635, 1582, 1446, 1383, 1312, 1146, 1076, 727 and 686; m/z(%) 374 (M^+,4), 233(36), 232(13), 231(11), 195(11), 143(17), 141(33), 126(11), 125(88), 107(9), 97(8), 92(9), 91(63), 85(12), 83(39), 79(11), 78(17) and 77(100).

Diethyl methylenecyclohex-2-ene-5,5-dicarboxylate (5a).
After a reaction time of 24h and work up as described above diethyl hepta-1-ene-6-yne-4,4-dicarboxylate (500mg) afforded the product (366mg, 73%) as a colourless oil whose spectroscopic properties were identical with those described previously:[6] δ 5.86 (d, 1H, CH=), 5.62 (m, 1H, CH=), 4.83 (m, 2H, CH_2=), 4.19 (q, 4H, CH_2Me), 2.96 (d, 2H, CH_2CH=CH), 2.57 (s, 2H, CH_2C=), and 1.24 (t, 6H, 2 x CH_2Me):

5,5-Diacetyl methylenecyclohex-2-ene (5b). Prepared from 4,4-diacetylhepta-1-ene-6-yne (500mg) by the general method with a reaction time of 24h. The product (310mg, 62%) was a colourless oil (Found: C, 73.85; H, 8.15. $C_{11}H_{14}O_2$ requires C, 774.15; H, 7.90%); δ 6.12 and 5.80 (2 x m, 2 x 1H, CH=CH), 4.95 (q, 2H, C=CH_2), 2.88 (t, 2H, CH_2C=), 2.66 (m, 2H, CH_2CH=), and 2.13 (s, 2 x 3H, Me); ν_{max} 3050, 2960, 2920, 2850, 1710 and 1620 cm^{-1}; m/z(%) 178 (M^+,6), 160(12), 136(17), 135(58), 93(16), 91(15) and 43(100).

Methyl 4,4-dimethylmethylenecyclohex-2-ene-5-carboxylate (5c). Prepared from methyl 3,3-dimethylhepta-1-ene-6-yne-4-carboxylate (540mg) by the general method with a reaction time of 6h. The product (450mg, 83%) was obtained as a colourless oil which underwent partial decomposition on distillation (molecular still), b.p. 35-40°C/1.0mmHg. Accurate mass: 180.1149. $C_{11}H_{16}O_2$ requires 180.1150; δ 6.11 (d, 1H, CH=$CHCH_2$), 5.72 (m, 1H, CH=$CHCH_2$), 4.99 and 4.83 (2 x s, 2 x 1H, =CH_2), 3.67 (s, 3H, OMe), 2.51 (m, 2H, $CHCO_2Me$ and HCHCH=CH), 2.33 (m, 1H, HCHCH=CH), and 1.16 and 1.13 (2 x s, 2 x 3H, Me); ν_{max} 3093, 3029, 2970, 1730, and 1638 cm^{-1}; m/z(%) 180 (M^+,21), 165(10), 122(10), 106(6), 105(23), 91(10), and 79(9).

N-Benzoyl-5-methylene-1,2,5,6-tetrahydropyridine (10a). Prepared from 4-benzoylaza hepta-1-ene-6-yne (500mg) by the general method with a reaction time of 30 min. After work up in the usual way the crude product was purified by preparative t.l.c. The product (66mg, 22%), was obtained as a yellow solid, m.p. 95-97°C (Found: C, 78.60; H, 6.50; N, 6.90. $C_{13}H_{13}NO$ requires C, 78.35; H, 6.60; N, 7.05%); δ 7.42 (m, 5H, ArH), 6.24 (br d, 1H, CH=$CHCH_2$), 5.73 (m, 1H, CH=$CHCH_2$), 4.85 (m, 2H, C=CH_2), and 4.21 and 3.96 (2 x m, 2 x 2H, NCH_2); ν_{max}(KBr) 3297, 3229, 2977, 2921, 2818, 2320, 1643 and 1603 cm^{-1}; m/z(%) 199 (M^+,51), 106(9), 105(100), 79(6), 78(7), and 77(40).

N-Benzyl-5-methylene-1,2,5,6-tetrahydropyridine (10b)
Prepared from 4-benzylazahepta-1-ene-6-yne (500mg) by the general method with a reaction time of 24h. The product (140mg, 28%) was a colourless oil, b.p. 40-50°C/0.1 mmHg (molecular still) (Found: C, 84.80; H, 7.50; N, 7.50. $C_{13}H_{15}N$ requires C, 84.30; H, 8.15; N, 7.55%); δ 7.57 (m, 5H, ArH), 6.23 (br d, 1H, CH=$CHCH_2$), 5.82 (m, 1H, CH=$CHCH_2$), 4.86 and 4.77 (2 x br s, 2 x 1H, C=CH_2), 3.62 (s, 2H, $ArCH_2$), 3.21 (s, 2H, NCH_2C=) and 3.09 (m, 2H, NCH_2CH=); ν_{max} 3289, 3082, 2924, 2342 and 1626 cm^{-1}; m/z(%) 185 (M^+,73), 184(45), 94(18), 92(22), 91(100), 67(6) and 65(17).

Palladium Catalysed Cyclisations

Diethyl 1,2-bis(methylene)cyclopentane-4,4-dicarboxylate (2, R=R^1=CO_2Et).
(a) A mixture of diethyl allyl(prop-2-ynyl)malonate (1.0g, 4.2 x 10^{-3}mol), palladium acetate (47mg, 2 x 10^{-4}mol) and triphenylphosphine (110mg, 4.2 x 10^{-4}mol) was boiled under reflux in acetonitrile (50ml) under an atmosphere of nitrogen for 30 min. The solvent was removed under reduced pressure and the residue chromatographed on alumina eluting with 3:1 v/v petroleum ether-ether. The product (776mg, 78%) was obtained as a colourless oil whose spectroscopic properties were identical to those described previously.[6]
(b) The reaction was repeated on the same scale but with the addition of piperidine (36mg, 4.2 x 10^{-4}mol) and formic acid (19mg, 4 x 10^{-4}mol), and a reaction time of 1h. Work up as above afforded (2, R=R^1=CO_2Et) (380mg, 38%)

and (14) (85mg, 8.5%). The latter compound had identical spectroscopic properties to those described previously.[1]

We thank Queen's University for support.

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