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LETTERS

Synthesis of quinol-4-ones and chroman-4-ones via a palladium-catalysed cascade carbonylation–allene insertion

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Abstract

Palladium(0)-catalysed termolecular queuing processes involving oxidative addition to aryl iodides followed by low pressure carbonylation, allene insertion and capture of the resulting π-allyl palladium(II) species by an internal O- or N-nucleophile occur in good yields. One-pot 3-methylene chromanone/quinolone synthesis–Michael addition–stereoselective reduction are also reported. © 2000 Elsevier Science Ltd. All rights reserved.

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Our recent development of a wide range of palladium-catalysed processes that allow incorporation of both allenes[1] and carbon monoxide[2] in polycomponent queuing cascades offers a general catalytic method for accessing quinolone and chromanone ring systems which display biological activity over a wide range of areas from antibacterials such as ciprofloxacin[3] to antifungals, e.g. **2a**,[4] and neurotrophic factors essential for survival and functioning of nerve cells such as recently reported neuchromenin.[5] As part of this programme we now report our results on three-component aryl iodide–carbon monoxide–allene (3+1+2)-cycloaddition cascade processes.

In contrast to Alper's recently reported[6] cascades of a similar type which were carried out at high pressures (20 atm) of carbon monoxide, we focused our studies on employing carbon monoxide at atmospheric pressure. A study of (3+1+2)-cycloaddition reactions of *o*-iodophenols and *N*-tosyl-*o*-iodoanilines was undertaken using allene (1 atm) and CO (1 atm) in a Schlenk tube.[7] The reactions of **1a** and **1b** occurred at 45°C in toluene in the presence of 5 mol%

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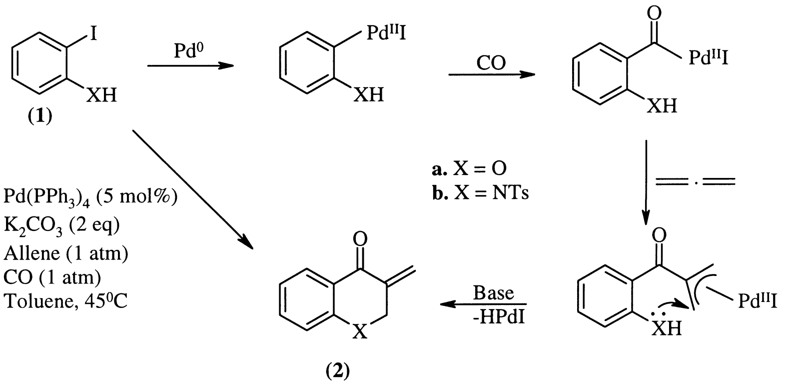
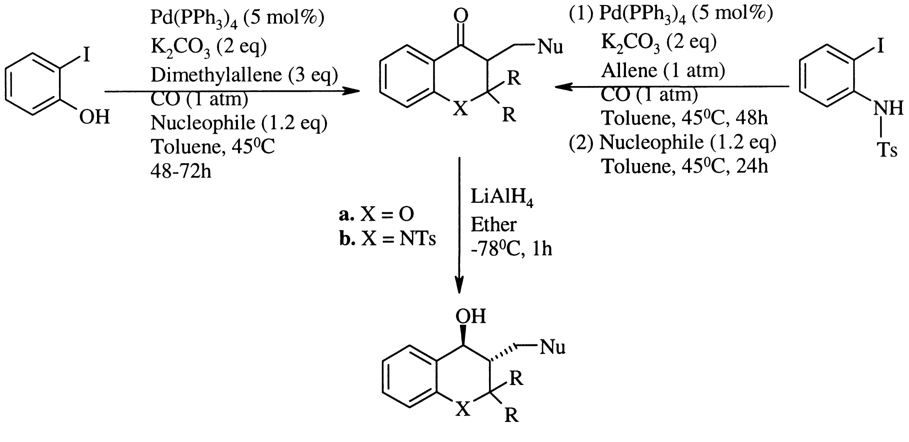


Scheme 1.

Pd(PPh$_3$)$_4$ and K$_2$CO$_3$ (2 equiv.) over 16 and 35 h, respectively, to afford **2a** (70%) and **2b** (55%) (Scheme 1).

These reactions are examples of termolecular queuing processes in which four functional moieties, namely the aryl iodide, the nucleophile (OH or NHTs), CO and the allene, are queuing to react at the metal centre. In the first step of the catalytic cycle, the palladium(0) catalyst undergoes oxidative addition to the aryl iodide bond followed by coordination and insertion of CO. The acylpalladium(II) intermediate adds to the allene at the central carbon atom to furnish a π-allylpalladium(II) species which undergoes nucleophilic attack by the internal nucleophile to give the enone product.

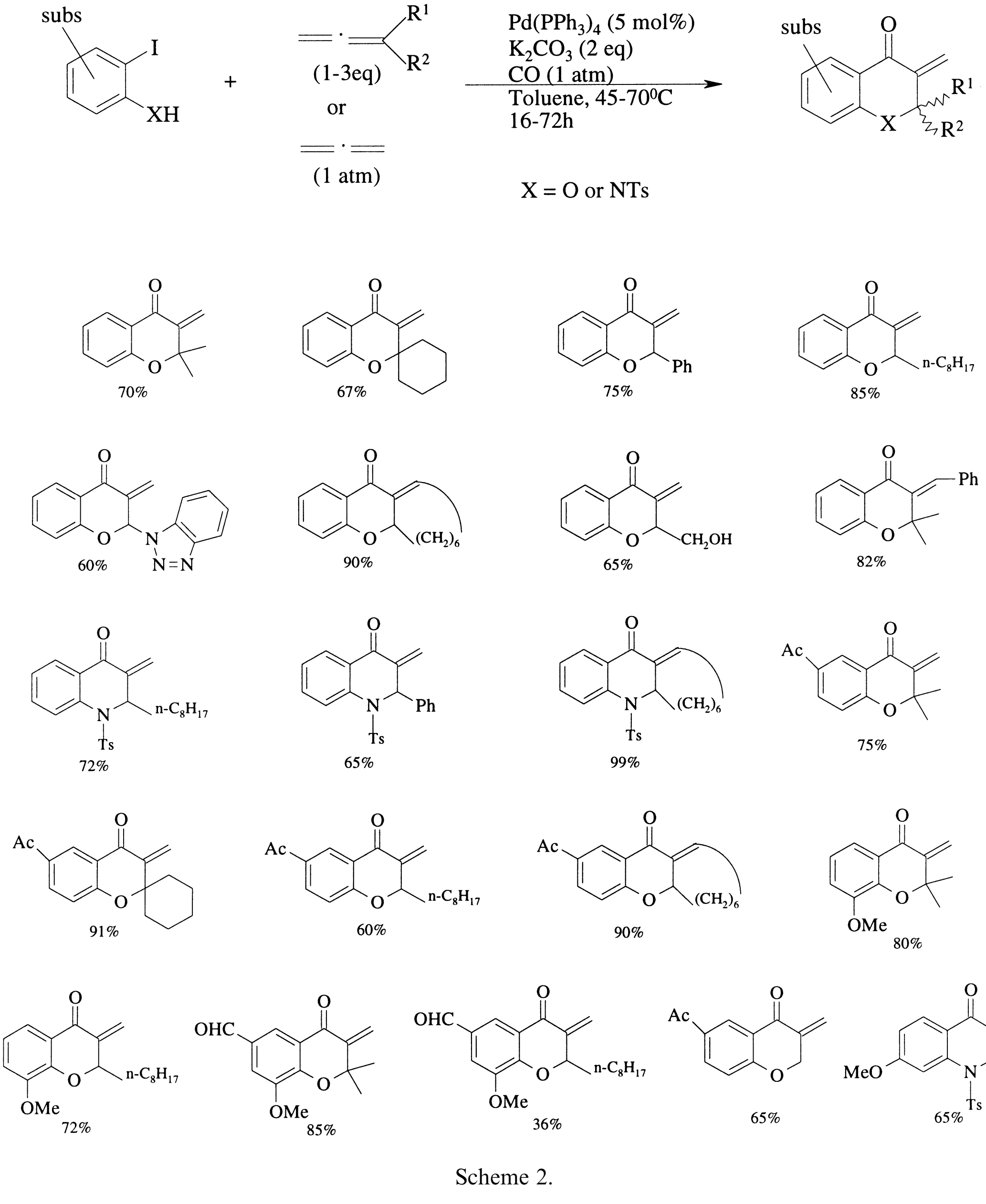


Scheme 3.

The (3+1+2)-cycloaddition tolerates substituents on both the allene and the aryl iodide allowing access to an array of heterocycles with *s-cis* enone moieties (Scheme 2).

The creation of the conformationally locked *s-cis* enone system in the quinolones and chromanones offers opportunities for substantial further synthetic elaboration. A study of one-pot chromanone synthesis–Michael addition was undertaken using *o*-iodophenol, nucleophile (1.2 equiv.), dimethylallene (3 equiv.) and CO (1 atm) in a Schlenk tube. The reactions occurred at

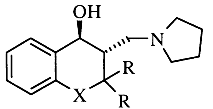
45°C in toluene in the presence of $Pd(PPh_3)_4$ (5 mol%) and K_2CO_3 (2 equiv.) over 48–72 h to afford the Michael adducts. One-pot quinolone synthesis–Michael addition was performed in a slightly different manner. (3+1+2)-Cycloaddition reaction of *N*-tosyl-*o*-iodoaniline, CO (1 atm) and allene (1 atm) was allowed to proceed for 48 h and CO was released before the addition of the nucleophile (1.2 equiv.). The subsequent Michael addition was completed after a further 24 h (Scheme 3). Both aliphatic and heteroaromatic *N*-nucleophiles were effective and in the case of 1,2,4-triazole only the 1-substituted triazole was observed. The Michael adducts proved sensitive to retro-Michael addition and so they were reduced by $LiAlH_4$ in ether[8] at –78°C for 1 h, without prior isolation, to give the corresponding γ-aminoalcohols (Table 1) as single stereoisomers.



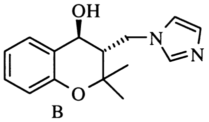
Scheme 2.

Table 1
One-pot chromanone/quinolone synthesis–Michael addition–reduction

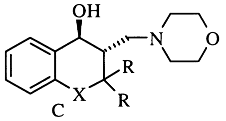
Nucleophile	γ-Aminoalcohol	Yield(%)[a]
Pyrrolidine	A	X = O, R = Me, 44 X = NTs, R = H, 23
Imidazole	B	51
Morpholine	C	X = O, R = Me, 46 X = NTs, R = H, 21
1,2,4-Triazole	D	X = O, R = Me, 50 X = NTs, R = H, 25



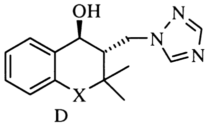
A



B



C



D

a. Overall yield

The results reported herein demonstrate efficient termolecular queuing cascades employing CO (1 atm). The one-pot formation of γ-aminoalcohols involves the formation of four bonds, two stereocentres and one ring. Further synthetic opportunities offered by the 3-methylene-4-quinolone/chromanone systems are elaborated in the accompanying communication.[9]

Acknowledgements

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References

1. Grigg, R.; Sridharan, V.; Terrier, C. *Tetrahedron Lett.* **1996**, *37*, 4221–4224; Grigg, R.; Savic, V. *Tetrahedron Lett.* **1996**, *37*, 6565–6568.
2. Grigg, R.; Redpath, V.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429–4432.
3. Grohe, K. *Chem. in Brit.* **1992**, 34–36; Wentland, M. P.; Cornett, J. B. *Ann. Rpt. Med. Chem.* **1985**, *20*, 145–154.
4. Ward, F. E.; Garling, D. L.; Buckler, R. T.; Lawer, D. M.; Cummings, D. P. *J. Med. Chem.* **1981**, *24*, 1073–1077.
5. Hayakawa, Y.; Yamamoto, H.; Tsuge, N.; Seto, H. *Tetrahedron Lett.* **1996**, *37*, 6363–6364.
6. Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566–1567.
7. Reactions were carried out with magnetic stirring in a Schlenk tube since allene diffuses readily through an ordinary balloon.
8. Risch, N.; Esser, A. *Liebigs Ann. Chem.* **1992**, 233–237.
9. Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Washington, M. L.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7129–7133.