Pergamon

TETRAHEDRON LETTERS

Tetrahedron Letters 44 (2003) 403–405

Diastereo- and regioselective palladium–indium bimetallic cyclisation–Barbier-type allylation cascades

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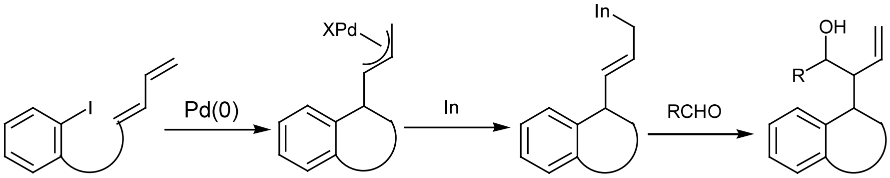
Received 27 May 2002; revised 30 September 2002; accepted 25 October 2002

Abstract—A new *diastereo*-and *regio*selective Pd/In bimetallic cascade process which assembles three contiguous chiral centres is described. Pd(0)-catalysed cyclisation of aryl iodides onto proximate 1,3-dienes generates π-allylpalladium(II) species, transmetallation with indium and subsequent Barbier-type addition to aldehydes affords heterocyclic homoallylic alcohols. © 2002 Elsevier Science Ltd. All rights reserved.

Allylation of carbonyl compounds is an important synthetic transformation and indium has emerged as the metal of choice to mediate these reactions.[1] We have previously described multi-component cascade reactions involving transmetallation of π-allylpalladium(II) species generated from allenes and aryl iodides with indium and subsequent addition of the allylindium species to aldehydes and imines.[2–5] Transmetallation of allenylpalladium(II)[6] and conventionally generated π-allylpalladium(II) species by indium salts have also been reported by others.[7–9]

In this communication we report a new diastereo- and regioselective bimetallic cascade reaction involving the palladium-catalysed cyclisation of aryl iodides onto proximate 1,3-dienes to generate a π-allylpalladium(II) complex.[10] Transmetallation by indium results in a nucleophillic allylindium species which subsequently undergoes Barbier-type addition to aldehydes affording complex homoallylic alcohols with three contiguous chiral centres (Scheme 1). Thus **1a** (1 mmol) reacts (DMF, 80°C, 24 h) with *p*-anisaldehyde (1.5 mmol) in the presence of indium (100 mesh powder, 1.5 mmol) and a catalytic system comprising Pd(OAc)$_2$ (10 mol%) and tris(2-furyl)phosphine (20 mol%) to afford isoindolinone **8** as a 3:1 mixture of diastereoisomers in 52% yield (Table 1). The relative stereochemistry of the major diastereoisomer has been determined by X-ray crystallography[11] (Fig. 1) and can be rationalised by employing Zimmerman–Traxler transition states (Fig. 2). The stereochemistry of the minor diastereoisomer is currently under investigation but has tentatively been assigned on the basis that it is the only other isomer possible if the large group of the aldehyde is fixed equatorially in the chair transition state. Modification of the benzyl group to a *n*-butyl group resulted in a slight improvement in the diastereoselectivity (Table 1, entry 2). A variety of aldehydes were successfully incorporated into the cascade in moderate to good yield (Table 1, entries 2–7) and their structure had little affect



Scheme 1.

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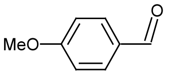
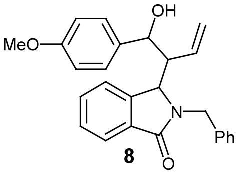
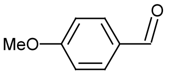
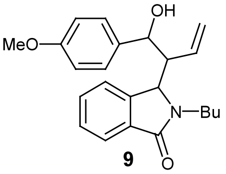
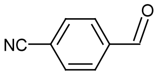
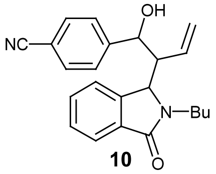
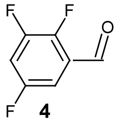
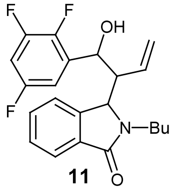
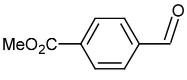
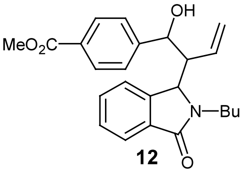
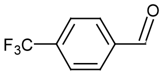
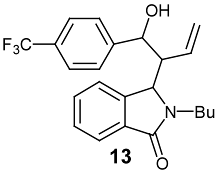
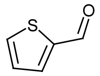
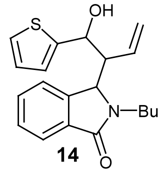
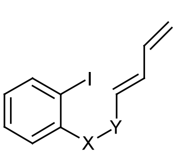
PII: S0040-4039(02)02428-0

Table 1.

Entry	Substrate	Aldehyde	Product	d.r.	Yield(%)
1	**1a**	 **2**	 **8**	75:25	52
2	**1b**	 **2**	 **9**	83:17	52
3	**1b**	 **3**	 **10**	81:19	75
4	**1b**	 **4**	 **11**	83:17	49
5	**1b**	 **5**	 **12**	79:21	58
6	**1b**	 **6**	 **13**	80:20	55
7	**1b**	 **7**	 **14**	81:19	53

on the ratio of diastereoisomers, which were easily separated by column chromatography. In all of the cases studied no products derived from β-hydride elimination have been observed. We next turned our attention to substrate **1c**. When this compound was subjected to the same reaction conditions as **1a**,**b**, the expected cascade ensued but with reduced levels of diastereoselectivity (Table 2, entries 1 and 2). Substrate **1d** was employed to study a 6-*exo*-*trig* cyclisation and afforded **17** as a 1.2:1 mixture of diastereoisomers in 56% combined yield (Table 2, entry 3).

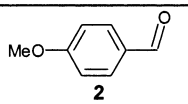
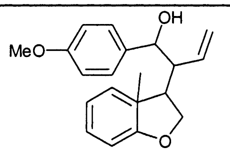
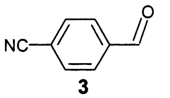
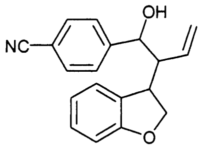
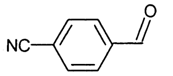
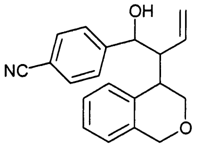


1

a: X = CO, Y = NCH_2Ph
b: X = CO, Y = NBu
c: X = O, Y = CH_2
d: X = CH_2O, Y = CH_2

Further work on these and related processes is in progress.

Table 2.

Entry	Substrate	Aldehyde	Product	d.r	Yield(%)
1	**1c**	 **2**	 **15**	54:46	48
2	**1c**	 **3**	 **16**	56:44	51
3	**1d**	 **3**	 **17**	55:45	56

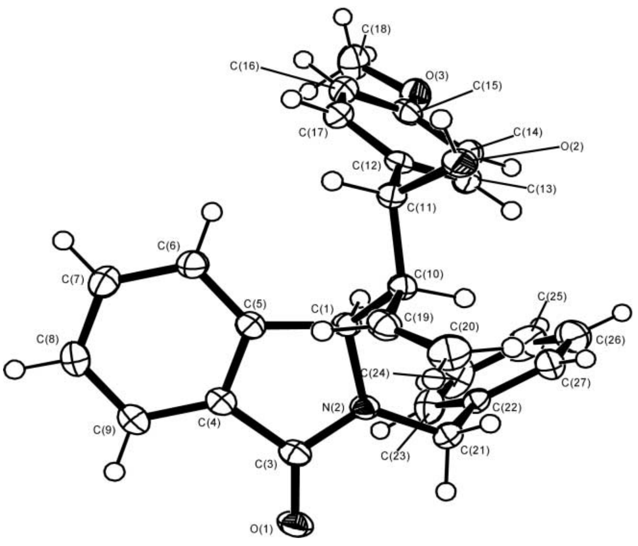


Figure 1.

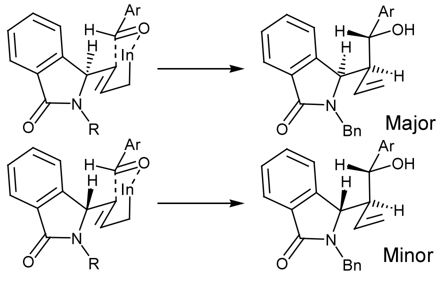


Figure 2.

Acknowledgements

We thank the University of Leeds and GlaxoSmith-Kline for support.

References

1. Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149–11176.
2. Anwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. *Chem. Commun.* **2000**, 645–646.
3. Anwar, U.; Grigg, R.; Sridharan, V. *Chem. Commun.* **2000**, 933–944.
4. Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2002**, 1372–1373.
5. For a recent example of the Pd/In system, see: Kang, S. K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376–4379.
6. Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214–8219.
7. Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847–849.
8. Araki, S.; Hirashita, T.; Kawai, M.; Yamamura, H. *Chem. Commun.* **2001**, 387–388.
9. Araki, S.; Kameda, K.; Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* **2001**, *66*, 7919–7921.
10. Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297–7320.
11. Deposited at the Cambridge Crystallography Database Centre (CCDC number 186322).