

Palladium/Chiral Amine Co-catalyzed Enantioselective β -Arylation of α,β -Unsaturated Aldehydes

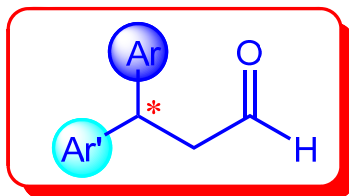
Reporter: Zhang-Pei Chen

Checker : Ran-Ning Guo

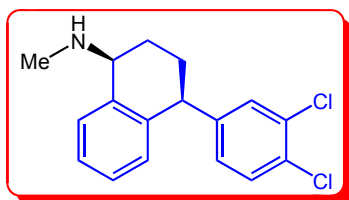
Date: 01/08/2013

A. Córdova, *et al.*
Angew. Chem. Int. Ed. **2013**, 52, 878.

The proposal of this issue



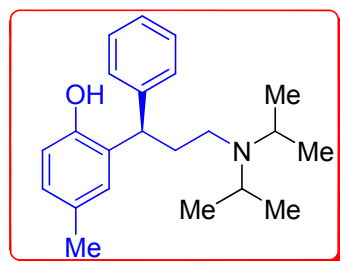
Enantioenriched chiral 3,3-diaryl-substituted aldehydes are valuable chiral building blocks for the preparation of numerous natural products and pharmaceuticals.



sertraline



In 2007, it was the most prescribed antidepressant on the U.S. retail market, with 29,652,000 prescriptions.



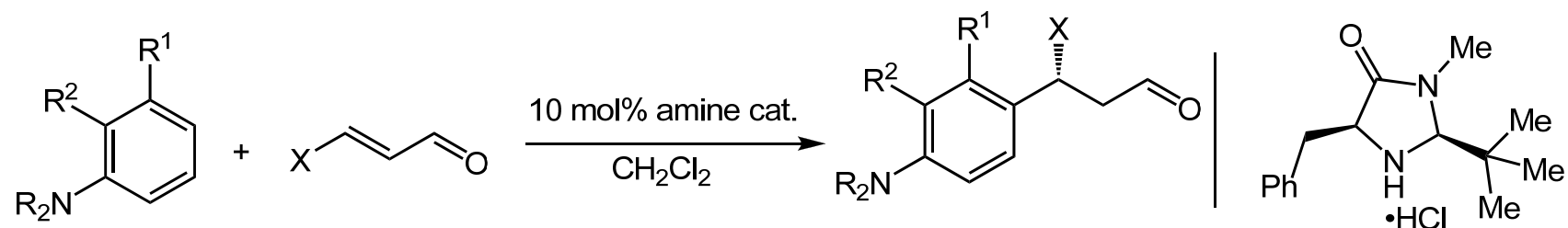
tolterodine



Tolterodine is an antimuscarinic drug that is used to treat urinary incontinence.

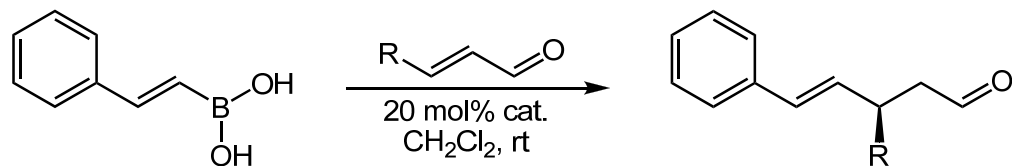
Some advances in this field

Amine-catalyzed addition of aromatic nucleophiles to enals

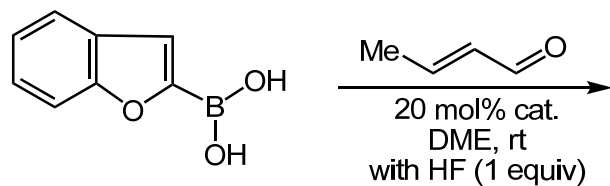


25 examples; 66~97% yield; 84~99% ee

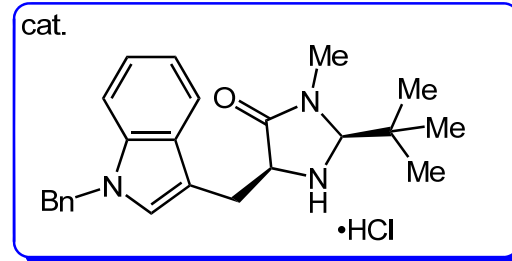
N. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, 124, 7894.



R = Me, no reaction
 R = CH₂OBn, 60% ee



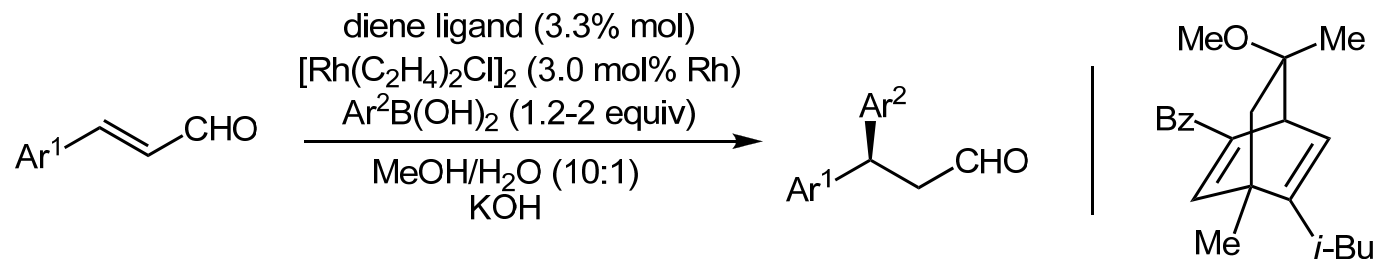
51% yield; 92% ee



S. Lee, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, 129, 15438.

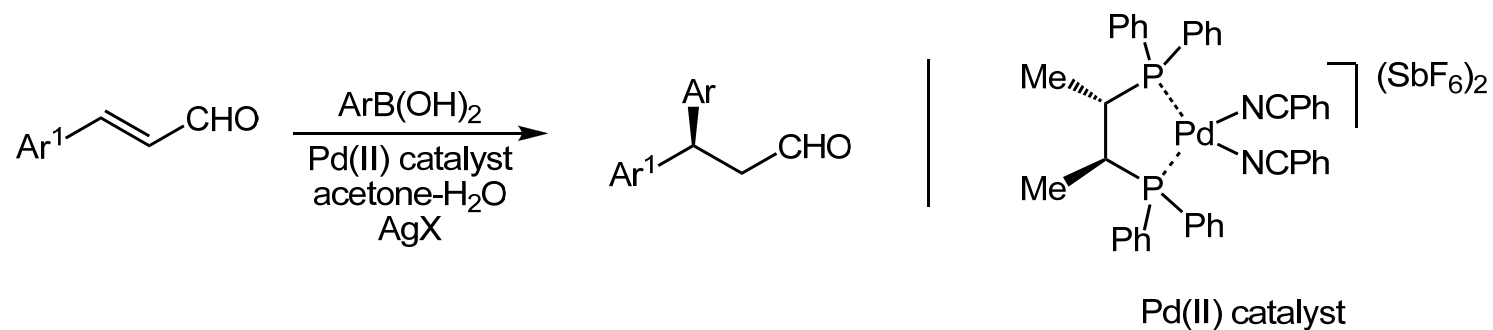
- ◆ This approach is restricted to electron-rich aromatic nucleophiles
- ◆ The low reactivity of electron-poor aromatic nucleophiles leads to no conjugate addition products

Metal catalyzed enantioselective conjugate addition (ECA)



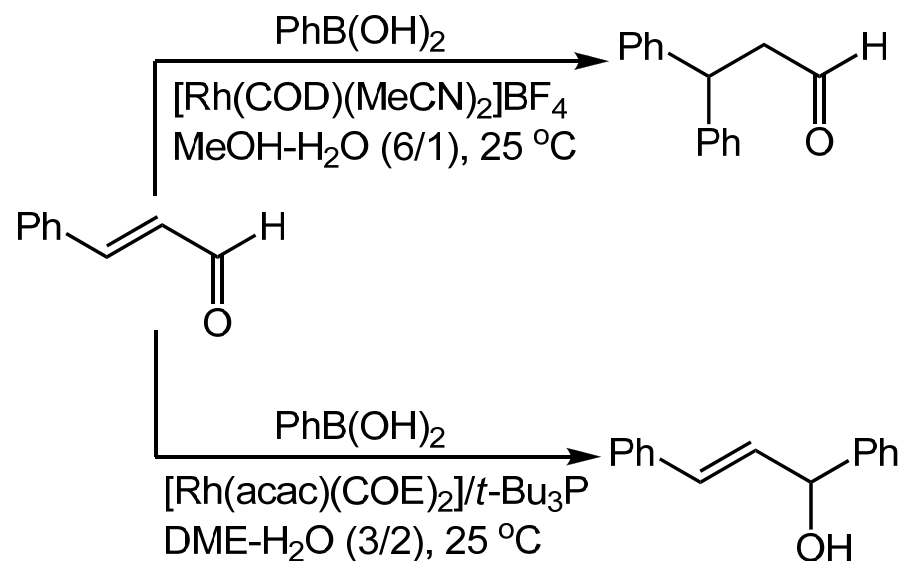
11 examples; 63~90% yield; 89~93% ee

J.-F. Paquin, C. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, 127, 10850.



18 examples; 29~89% yield; 88~94% ee

T. Nishikata, Y. Yamamoto, N. Miyaura, *Tetrahedron Lett.* **2007**, 48, 4007.



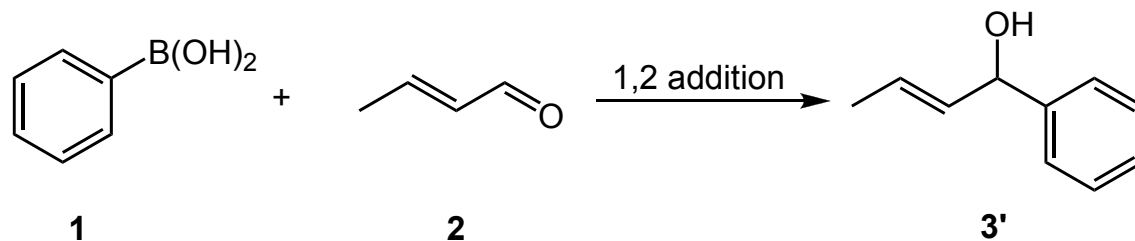
1,4-Addition versus 1,2-Addition

M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450.

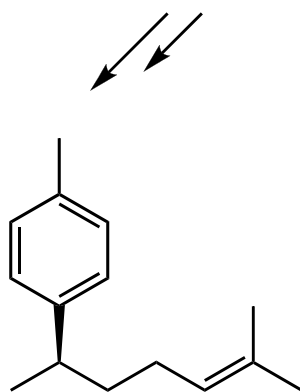
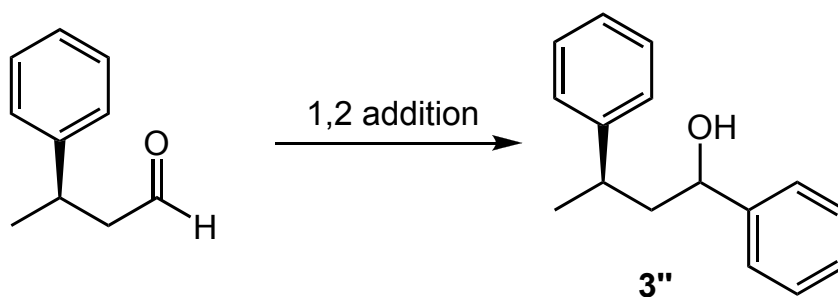
There are very few examples of catalytic asymmetric conjugate additions of aryl boronic acids to 3-alkyl-substituted enals.

This is due to the high reactivity of aldehydes, which can undergo competitive 1,2 addition either to the starting enal (regioselectivity) or to the product (enal vs. product, chemoselectivity).

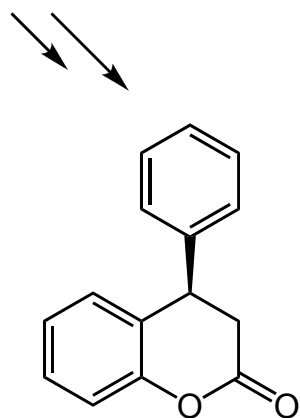
The idea of the author



metal catalyst
chiral-amine catalyst



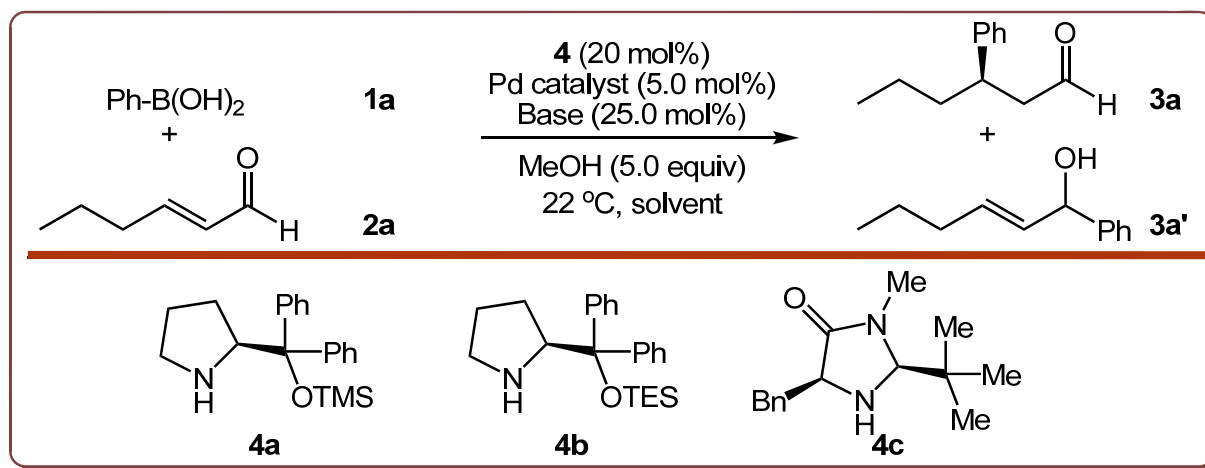
(*R*)-(-)-curcumene



4-arylchroman-2-one

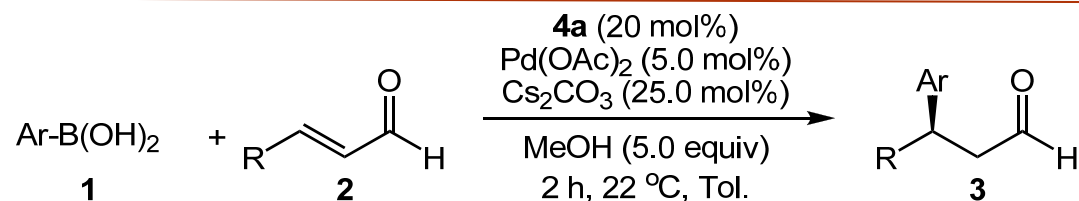
- ◆ Chiral amine to lower the LUMO of an enal 2
- ◆ In combination with transition-metal-catalysis

Conditions screening



| Entry | Cat. | Metal salt | Base | Solvent | <i>t</i> | Conv. [%] | Ratio 3a/3a' | e.r. |
|-------|------|------------------------------------|---------------------------------|---------|----------|-----------|--------------|-------|
| 1 | 4a | Pd(OAc) ₂ | - | Tol. | 8 | 10 | n.d. | n.d. |
| 2 | 4a | Pd(OAc) ₂ | Cs ₂ CO ₃ | Tol. | 2 | 98 | >99:1 | 87:13 |
| 3 | 4a | Pd(OAc) ₂ | Cs ₂ CO ₃ | DMF | 6 | <2 | n.d. | n.d. |
| 4 | 4a | Ni(PPh ₃) ₄ | Cs ₂ CO ₃ | Tol. | 8 | <2 | n.d. | n.d. |
| 5 | 4a | Cu(OTf) ₂ | Cs ₂ CO ₃ | Tol. | 8 | <2 | n.d. | n.d. |
| 6 | 4b | Pd(OAc) ₂ | Cs ₂ CO ₃ | Tol. | 3 | 98 | >99:1 | 87:13 |
| 7 | 4c | Pd(OAc) ₂ | Cs ₂ CO ₃ | Tol. | 8 | <2 | n.d. | n.d. |
| 8 | 4a | Pd(PPh ₃) ₄ | Cs ₂ CO ₃ | Tol. | 8 | 30 | 0:100 | n.d. |

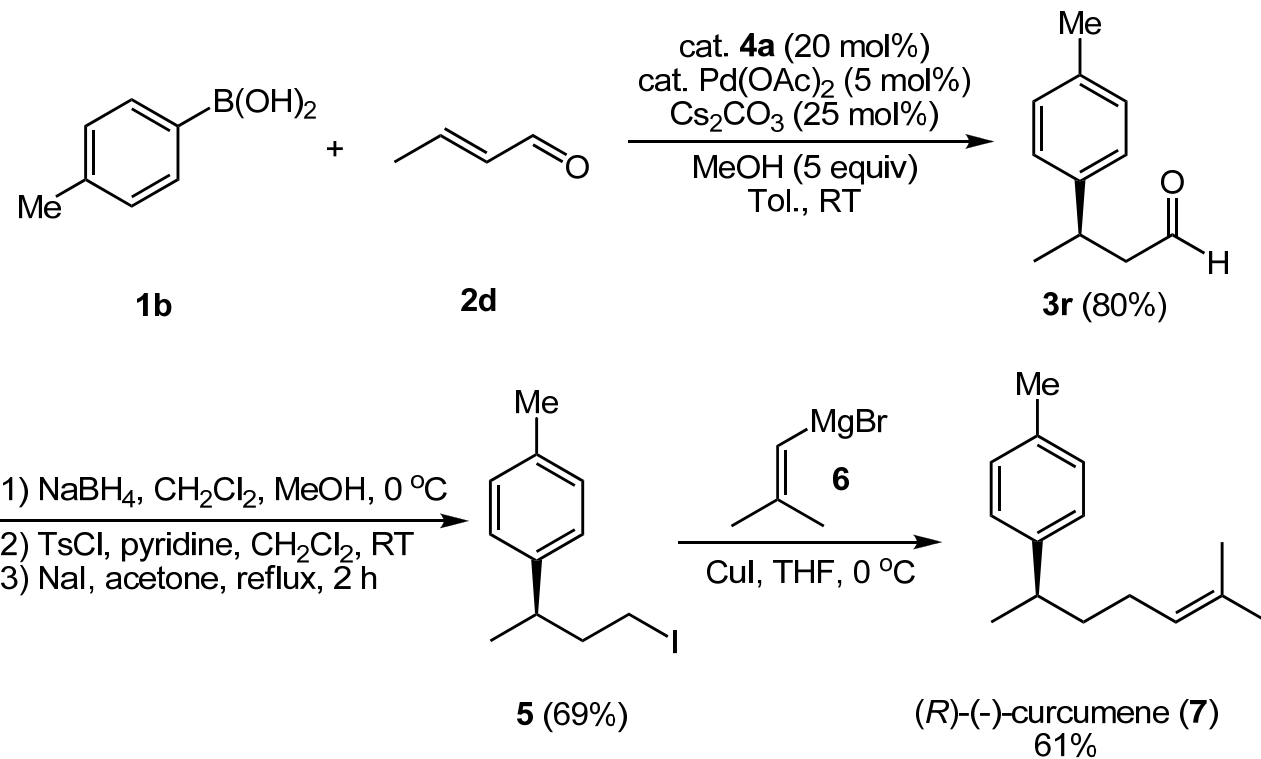
Substances scope

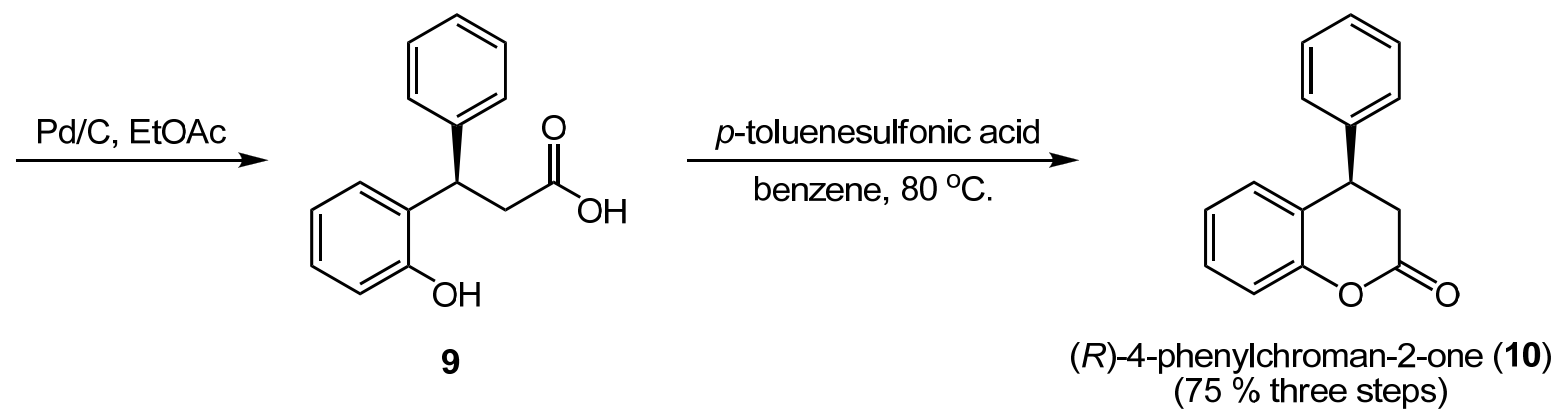
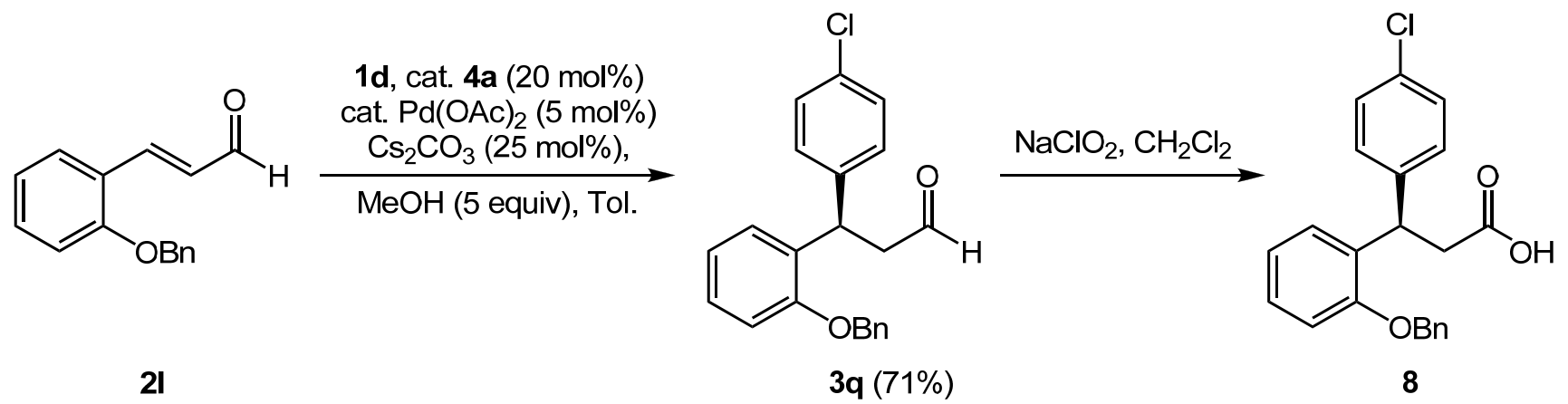


| Entry | 1, Ar | 2, R | Product | yield[%] | e.r. |
|-------------------|---|--|-----------|----------|-------|
| 1 | 1a , Ph | 2a , <i>n</i> -Pr | 3a | 79 | 87:13 |
| 2 | 1b , 4-CH ₃ C ₆ H ₄ | 2a , <i>n</i> -Pr | 3b | 80 | 86:14 |
| 3 | 1c , 4-CF ₃ C ₆ H ₄ | 2a , <i>n</i> -Pr | 3c | 81 | 87:13 |
| 4 | 1d , 4-ClC ₆ H ₄ | 2c , Et | 3g | 78 | 87:13 |
| 5 ^[a] | 1d , 4-ClC ₆ H ₄ | 2d , Me | 3h | 80 | 83:17 |
| 6 ^[b] | 1c , 4-CF ₃ C ₆ H ₄ | 2e , Ph | 3j | 79 | 93:7 |
| 7 ^[b] | 1d , 4-ClC ₆ H ₄ | 2e , Ph | 3k | 81 | 93:7 |
| 8 ^[c] | 1a , Ph | 2f , 4-MeOC ₆ H ₄ | 3m | 75 | 92:8 |
| 9 ^[d] | 1a , Ph | 2g , 4-ClC ₆ H ₄ | 3n | 76 | 95:5 |
| 10 ^[e] | 1a , Ph | 2i , 2-BnOC ₆ H ₄ | 3p | 70 | 90:10 |
| 11 ^[e] | 1d , 4-ClC ₆ H ₄ | 2i , 2-BnOC ₆ H ₄ | 3q | 71 | 91:9 |

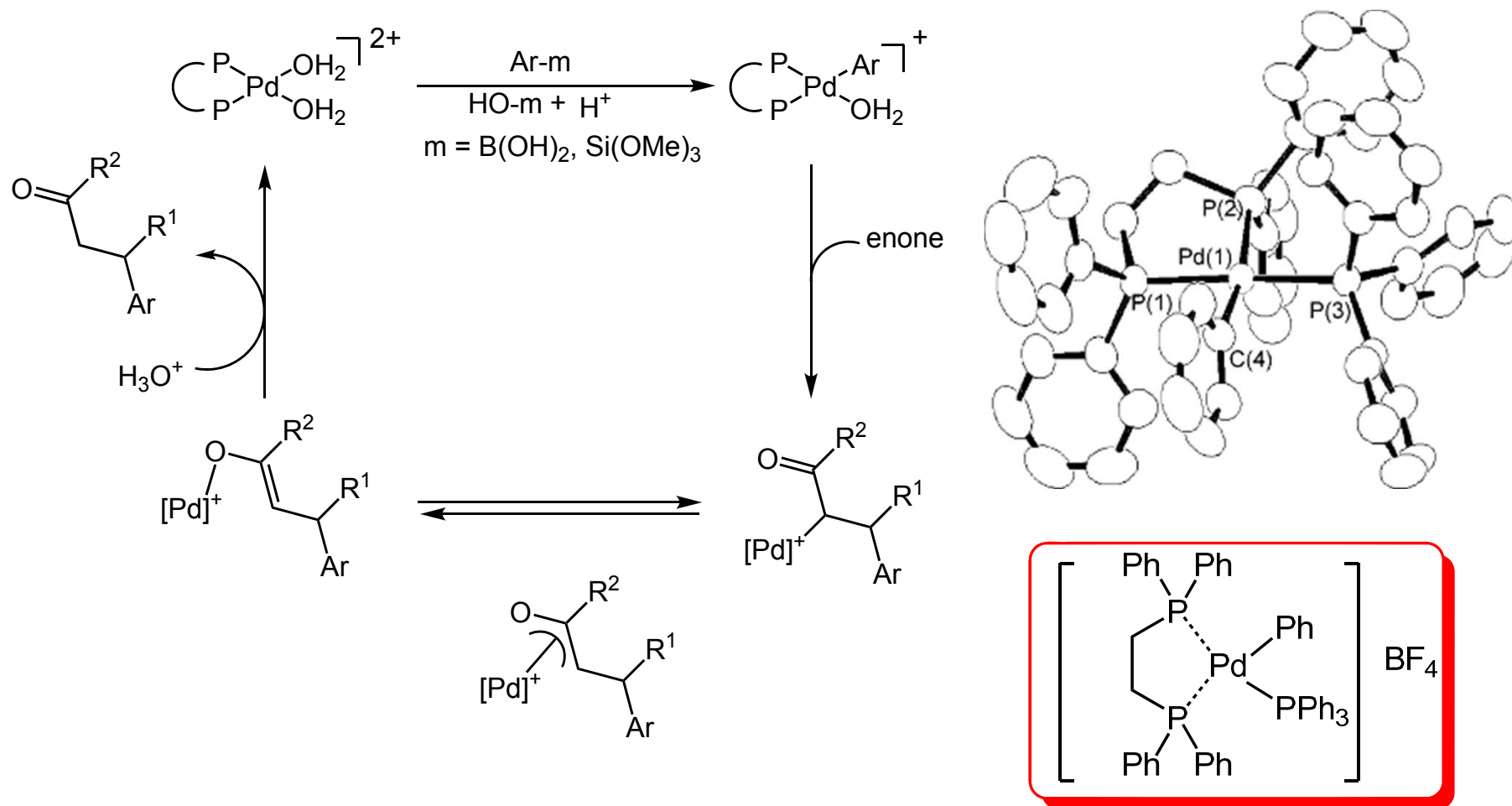
Under N₂ atmosphere, **1** (1.5 equiv), Pd(OAc)₂ (5 mol%), **4a** (20 mol%), Cs₂CO₃ (25 mol%), MeOH (5.0 equiv), and **2** (1 equiv) in toluene at 22 °C. Final concentration 0.20 M. [a] **1** (1.0 equiv), enal **2d** (2 equiv). [b] Reaction time was 3 h. [d] Reaction time was 6 h. Reaction time was 6 h. [e] Reaction time was 3 h and temperature 50 °C. No 1,2 addition products (**3'** or **3''**) were observed.

Representative Valuable Conversions of the Products

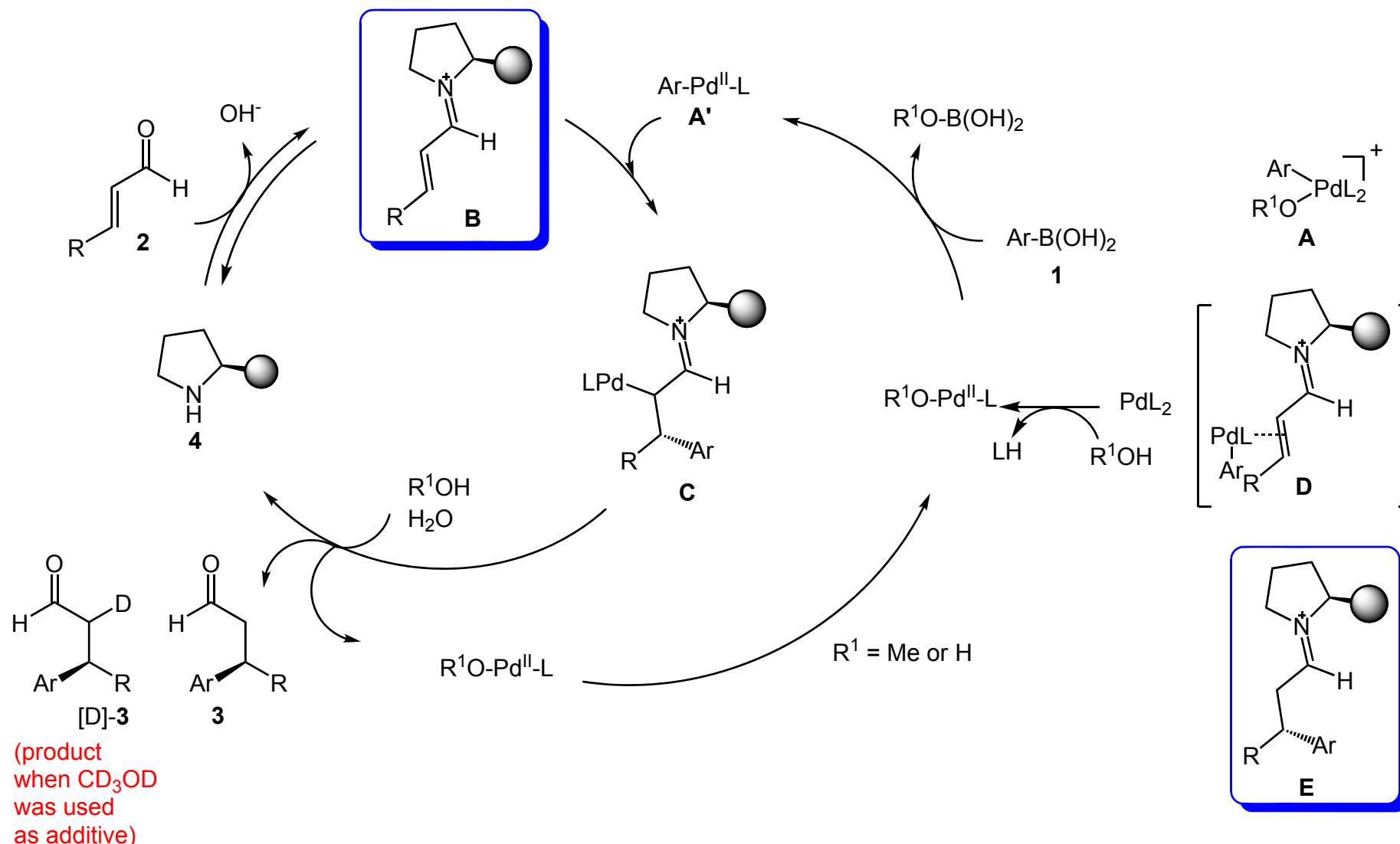




Proposed catalytic cycle



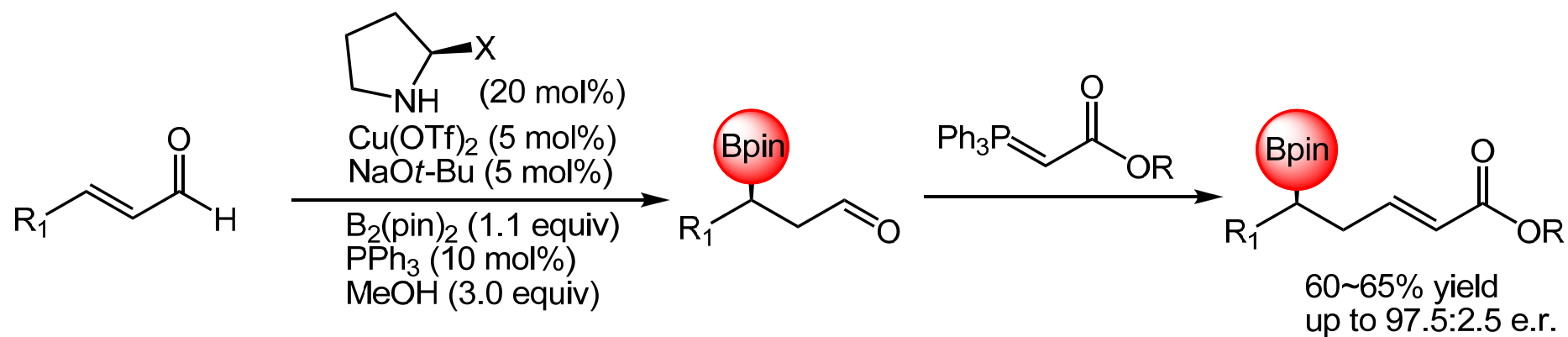
T. Nishikata, Y. Yamamoto, N. Miyaura, *Organometallics* **2004**, 23, 4317.

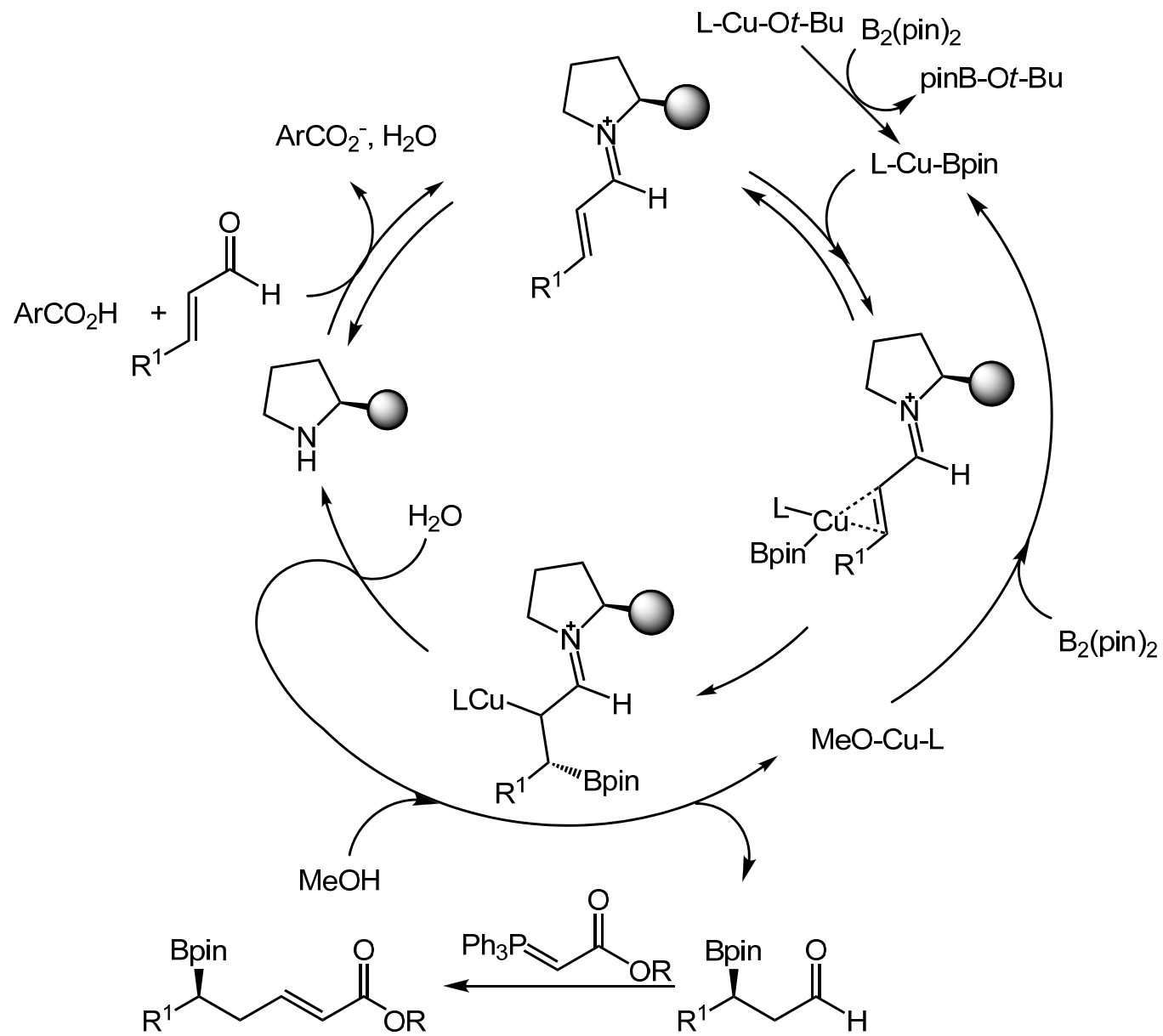


◆ iminium intermediates **B** and **E** was confirmed by direct HRMS

◆ MeOH was a proton source for the O-Pd bond cleavage of **C**

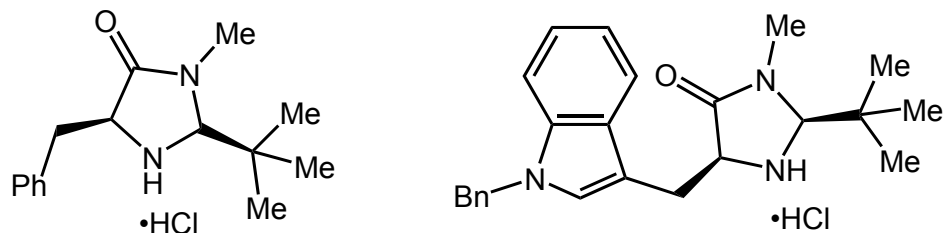
Organic and Metal synergistic catalysis



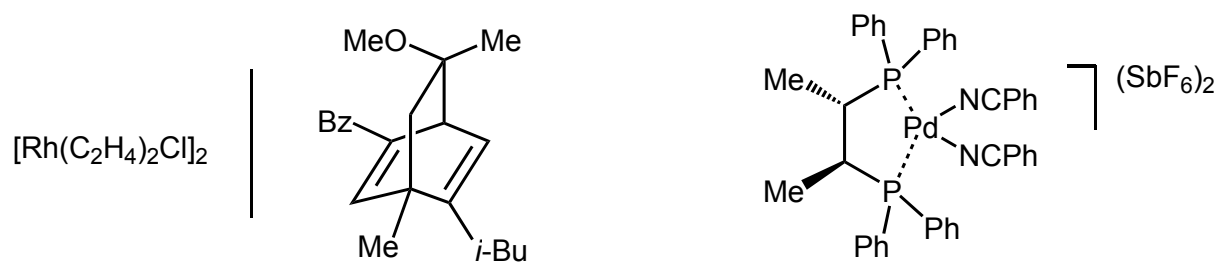


Summary

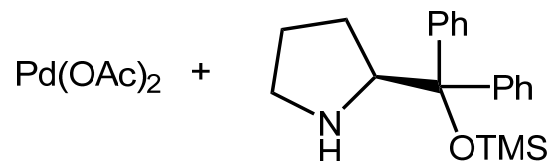
Amine-catalyzed addition of aromatic nucleophiles to enals



Metal catalyzed enantioselective conjugate addition (ECA)



Iminium activation with transition-metal-catalyzed nucleophilic activation



Enantioenriched chiral 3,3-diaryl-substituted aldehydes are valuable chiral building blocks for the preparation of numerous natural products and pharmaceuticals (e.g. 4-arylchroman-2-ones, sertraline, and tolterodine). However, asymmetric synthesis of these aldehydes is cumbersome and challenging, because little distinguishes the two arenes sterically or electronically, in particular, when the aryl moiety is substituted at the *para* position. One catalytic way to synthesize nonracemic 3,3-diarylpropanals and 3-alkyl-3-arylpropanals is the amine-catalyzed addition of aromatic nucleophiles to enals. However, this approach is restricted to electron-rich aromatic nucleophiles. In fact, the low reactivity of electron-poor aromatic nucleophiles leads to no conjugate addition products.

In summary, we have disclosed a co-catalyzed β -arylation of α,β -unsaturated aldehydes with aryl boronic acids by combining simple Pd and chiral amine catalysts. The reactions are highly 1,4-selective and the corresponding aldehyde products were obtained in high yields with good enantiomeric ratios (up to 95:5 e.r.). The co-catalyzed asymmetric β -arylation reaction allowed the use of both β -alkyl- and β -aryl-substituted aldehydes as acceptors. The reaction was employed for the short total syntheses of (*R*)-(-)-curcumene and (*R*)-4-phenylchroman-2-one. It should also serve as an efficient entry for diversity-oriented synthesis. Results in this area and other total synthesis will be disclosed in due course.