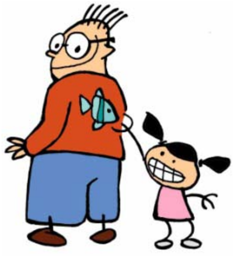
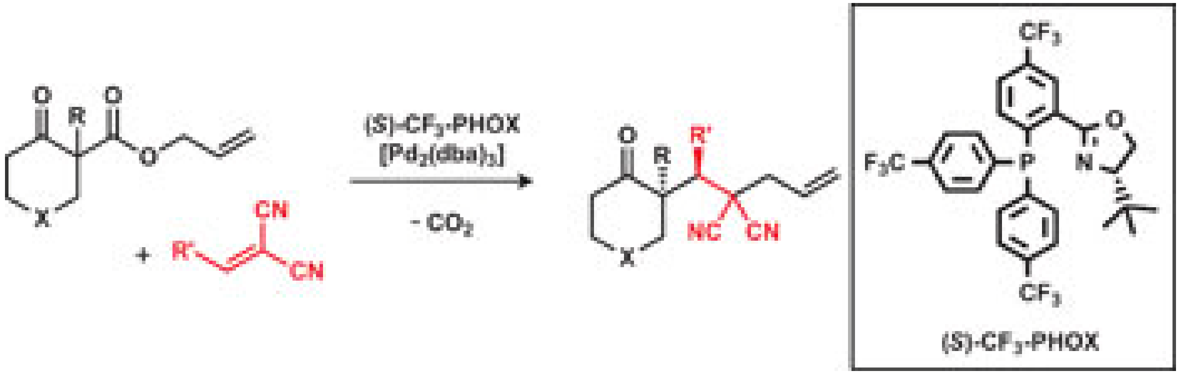
StéréO

iSm2 Institut des Sciences Moléculaires de Marseille UMR 6263



# A palladium-catalysed enolate alkylation cascade for the formation of adjacent quaternary and tertiary stereocentres



Streuff, J.; White, D.; Virgil, S.; Stoltz, B. *Nature Chem.* **2010**, *2*, 192-199.

RCC 01/04/2010

Damien Mailhol

# From the litterature…

organocatalysis

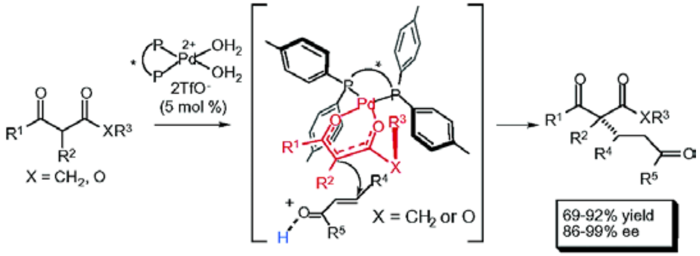
- Enantioselective α-functionalisation of carbonyl

  ⇒ IV$^{ary}$ and III$^{ary}$ vicinal stereocentres

- Only 2 **enantioselective transition-metal catalysed** examples published so far:

JACS COMMUNICATIONS

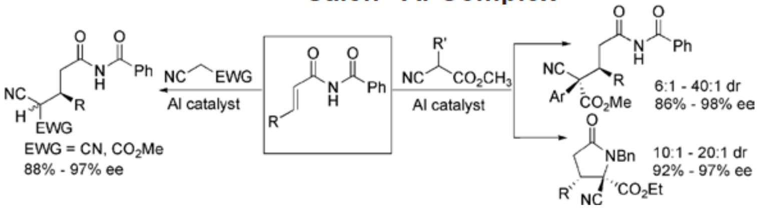
**Direct Generation of Nucleophilic Chiral Palladium Enolate from 1,3-Dicarbonyl Compounds: Catalytic Enantioselective Michael Reaction with Enones**



Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240-11241.

JACS COMMUNICATIONS

**Enantioselective Michael Additions to α,β-Unsaturated Imides Catalyzed by a Salen–Al Complex**

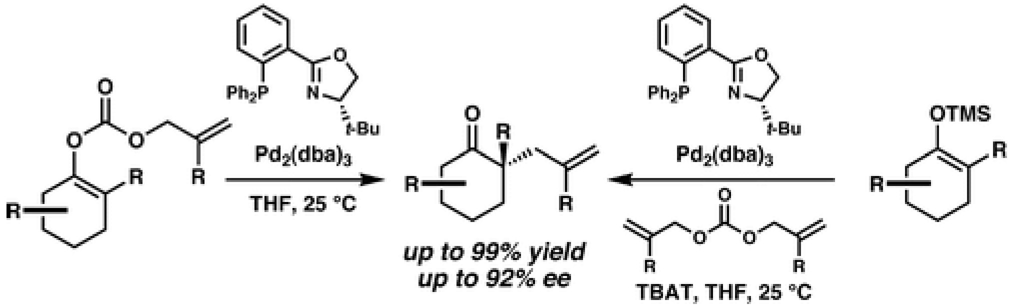


Taylor, S.; Jacobsen, E. *J. Am. Chem. Soc.* **2003**, *125*, 11204-11205.

# From the litterature…

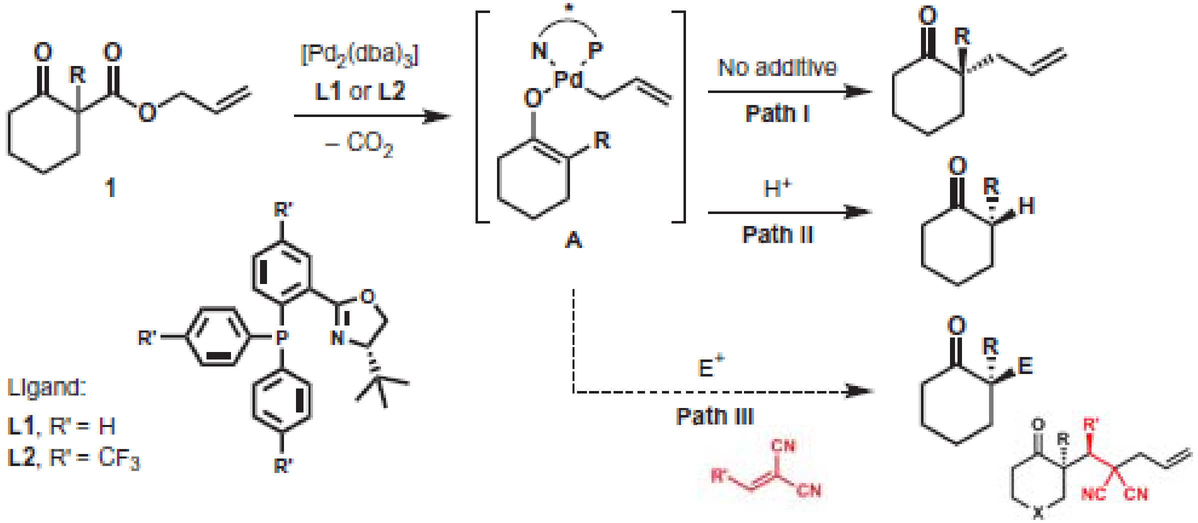
J|A|C|S COMMUNICATIONS

**The Enantioselective Tsuji Allylation**



Behenna, C.; Stoltz, B. *J. Am. Chem. Soc.* **2004**, 126, 15044-15045.

…to this work!



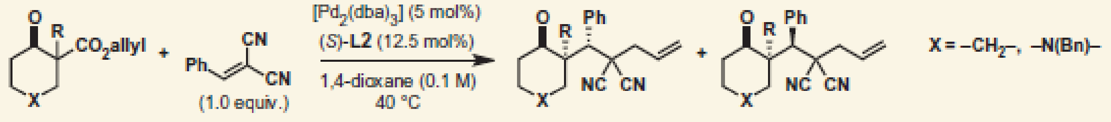
Mohr, J.; Behenna, C.; Harned, A.; Stoltz, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924-6927.

Mohr, J.; Nishimata, T.; Behenna, C.; Stoltz, B. *J. Am. Chem. Soc.* **2006**, *128*, 11348-11349.

Marinescu, S.; Nishimata, T.; Mohr, J.; Stoltz, B. *Org. Lett.* **2008**, *10*, 1039-1042.

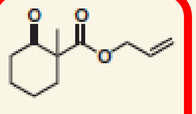
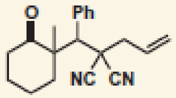
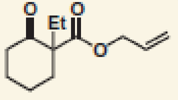
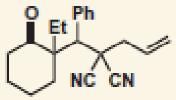
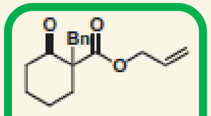
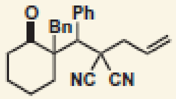
Patil, N.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991-6995.

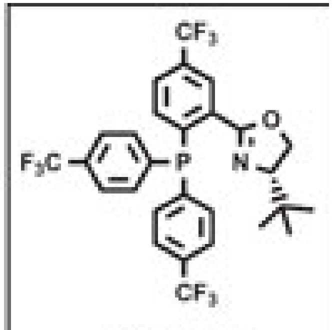
# Looking for β-ketoesters



**1a–h** **2a** **3a–h** **4a–h**

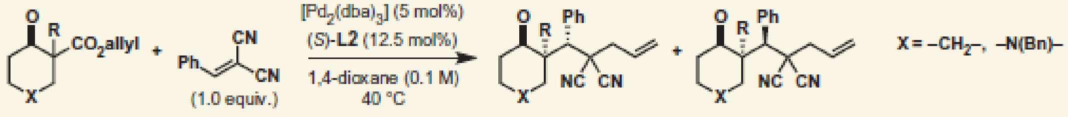
X = –CH$_2$–, –N(Bn)–

| Entry | Substrate | Product | Time (hours) | Yield (%)[*] | d.r. 3:4[†] | e.e. 3 (%) | e.e. 4 (%) |
|---|---|---|---|---|---|---|---|
| 1 | <br>**1a** | <br>**3a, 4a** | 24 | 99 | 1:6.1 | 77 | 87 |
| 2 | <br>**1b** | <br>**3b, 4b** | 48 | 91 | 1:3.5 | 95 | 99 |
| 3[‡] | | | 72 | 88 | 1:3.4 | 88 | 97 |
| 4 | <br>**1c** | <br>**3c, 4c** | 40 | 49 | 1:1.9 | 85 | 88 |
| 5[§] | | | 65 | 65 | 1:1.9 | 93 | 94 |

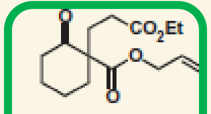
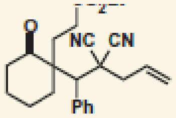
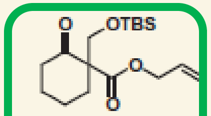
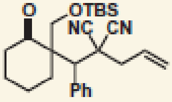
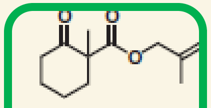
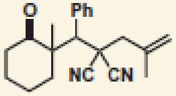
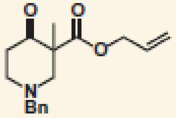
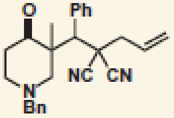
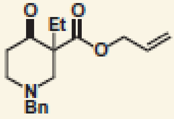
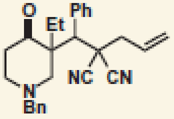


(*S*)-CF$_3$-PHOX

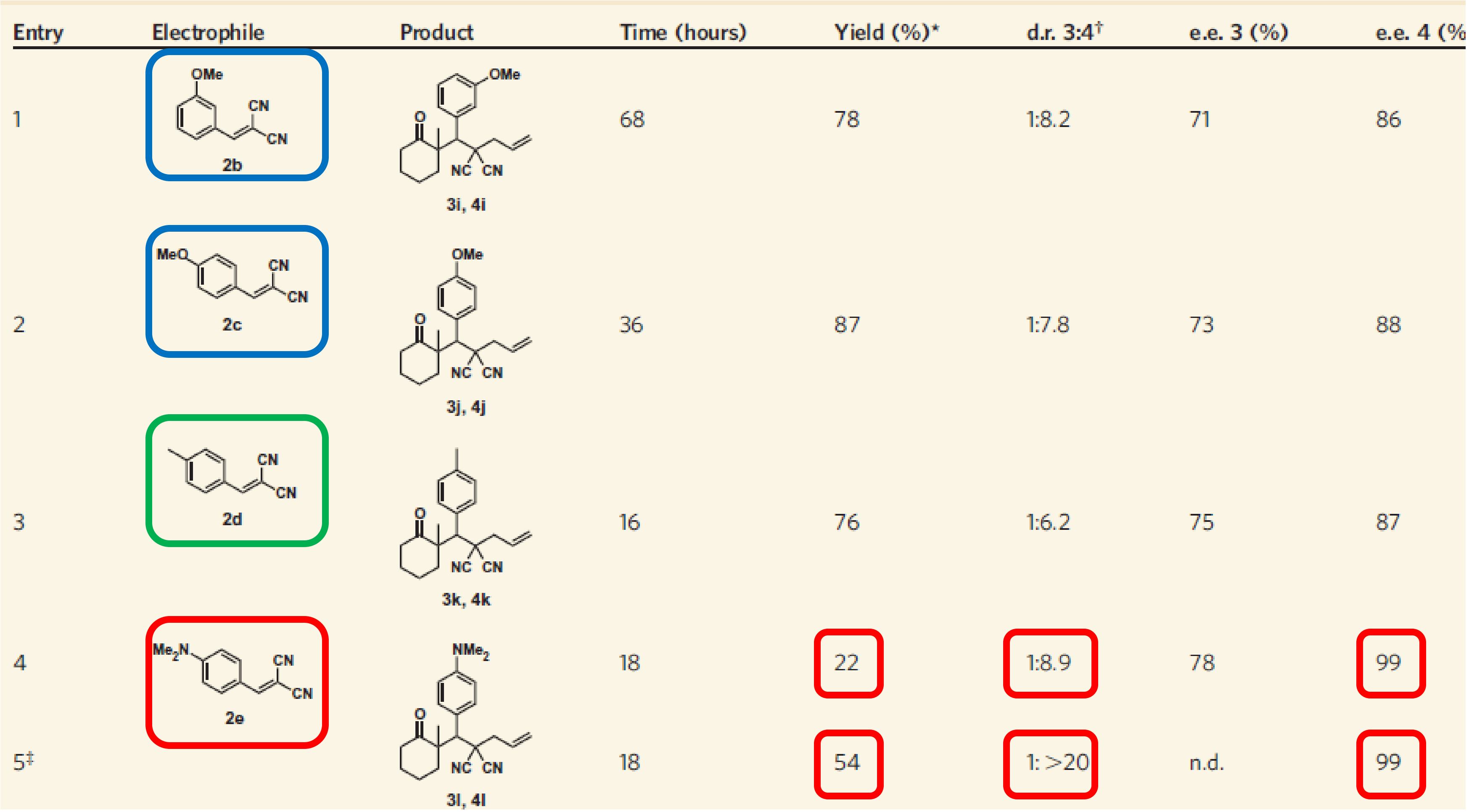
# Looking for β-ketoesters



1a–h 2a 3a–h 4a–h

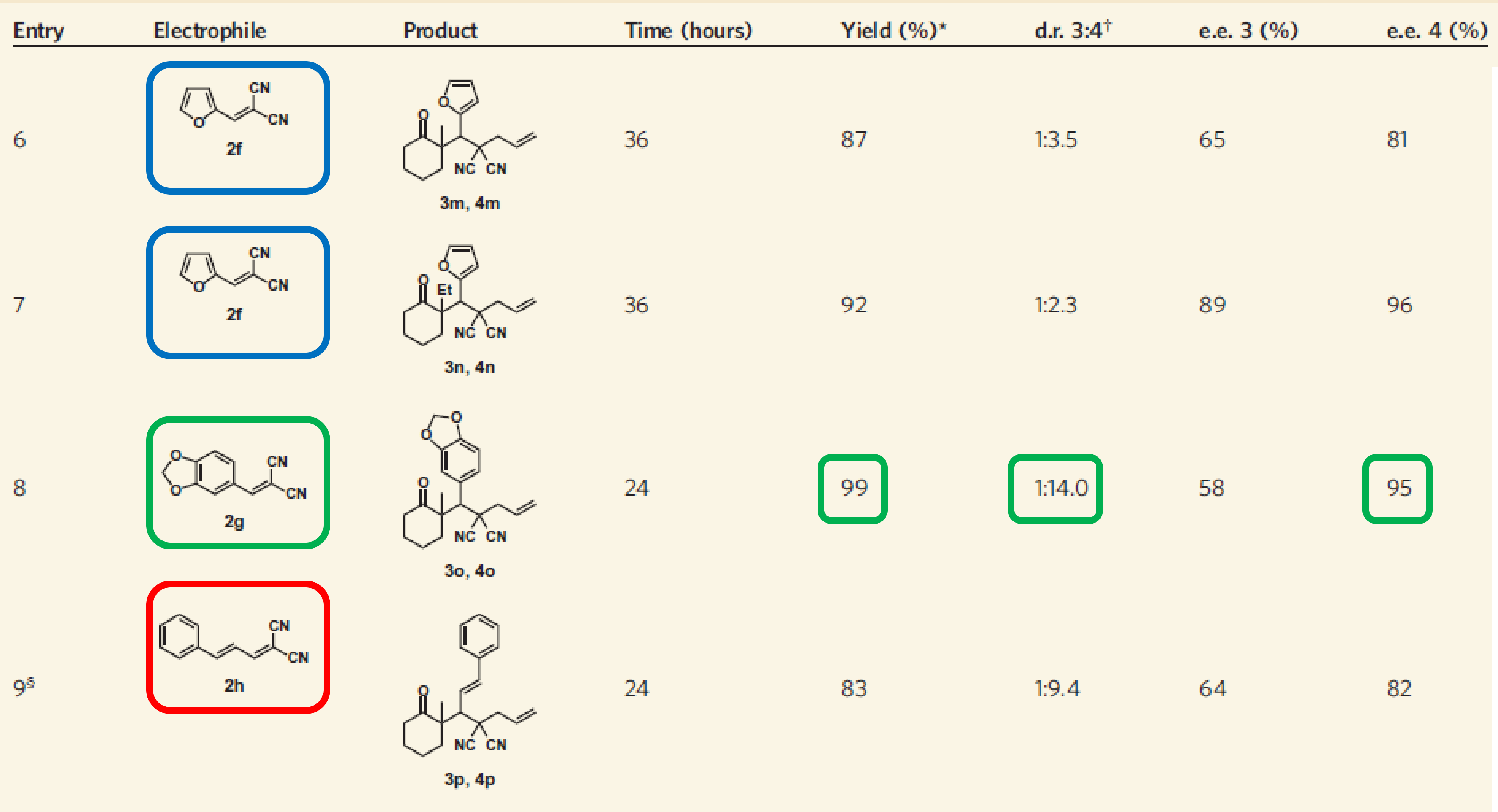
| Entry | Substrate | Product | Time (hours) | Yield (%)* | d.r. 3:4† | e.e. 3 (%) | e.e. 4 (%) |
|---|---|---|---|---|---|---|---|
| 6 |  1d |  3d, 4d | 24 | 56 | 1:3.3 | 82 | 89 |
| 7‖ |  1e |  3e, 4e | 24 | 56 | 1:1.3 | 69 | 70 |
| 8¶ |  1f |  3f, 4f | 72 | 57 | 1:2.4 | 75 | 81 |
| 9 |  1g |  3g, 4g | 20 | 97 | 1:>20 | - | 89 |
| 10 |  1h |  3h, 4h | 48 | 99 | 1:>20 | 71 | 97 |

# Exploration of electrophiles



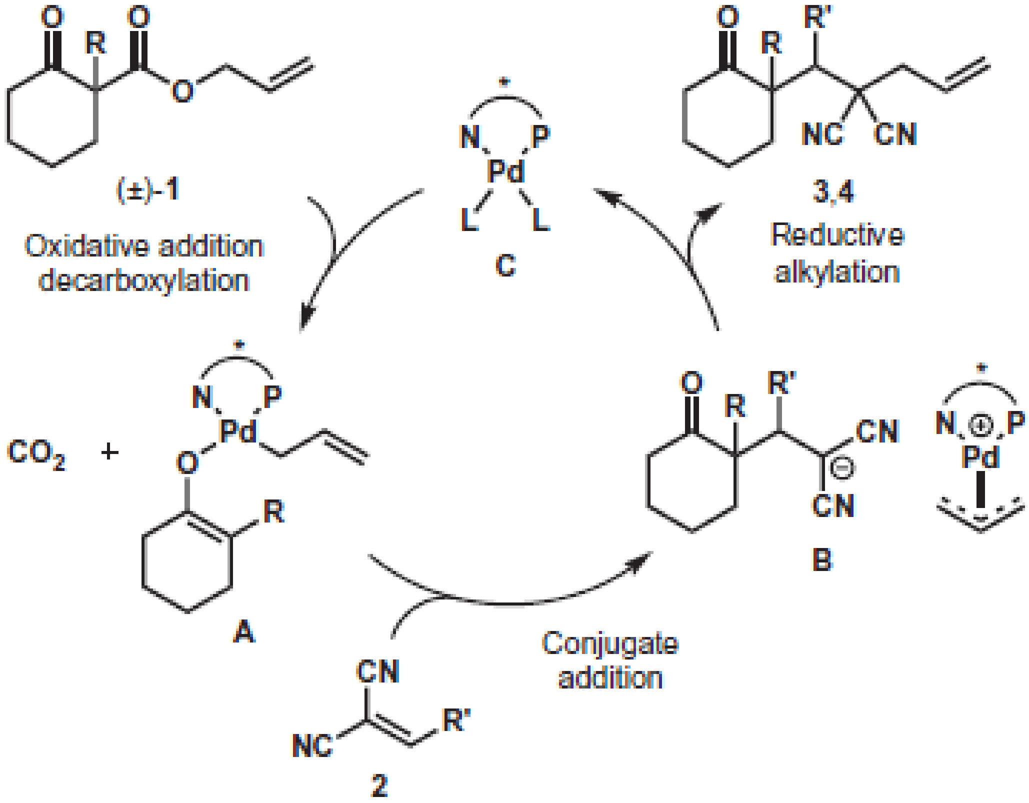
| Entry | Electrophile | Product | Time (hours) | Yield (%)[*] | d.r. 3:4[†] | e.e. 3 (%) | e.e. 4 (% |
|---|---|---|---|---|---|---|---|
| 1 | 2b | 3i, 4i | 68 | 78 | 1:8.2 | 71 | 86 |
| 2 | 2c | 3j, 4j | 36 | 87 | 1:7.8 | 73 | 88 |
| 3 | 2d | 3k, 4k | 16 | 76 | 1:6.2 | 75 | 87 |
| 4 | 2e | 3l, 4l | 18 | 22 | 1:8.9 | 78 | 99 |
| 5[‡] |  |  | 18 | 54 | 1: >20 | n.d. | 99 |

# Exploration of electrophiles

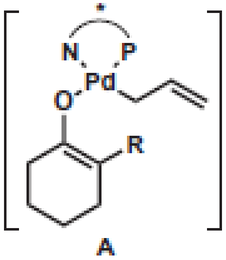


| Entry | Electrophile | Product | Time (hours) | Yield (%)[*] | d.r. 3:4[†] | e.e. 3 (%) | e.e. 4 (%) |
|---|---|---|---|---|---|---|---|
| 6 | 2f | 3m, 4m | 36 | 87 | 1:3.5 | 65 | 81 |
| 7 | 2f | 3n, 4n | 36 | 92 | 1:2.3 | 89 | 96 |
| 8 | 2g | 3o, 4o | 24 | 99 | 1:14.0 | 58 | 95 |
| 9[§] | 2h | 3p, 4p | 24 | 83 | 1:9.4 | 64 | 82 |

# Plausible simplified catalytic cycle



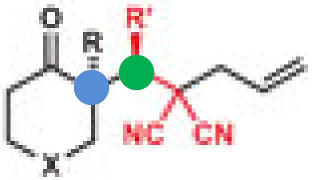
# In conclusion



Traping of a Pd-enolate by a prochiral activated Michael acceptor

- Higlhy enantio- and diastereoselective Pd-catalysed $\alpha$-alkylation process

- Asymmetric construction of densely functionalised molecules that possess an all-carbon quaternary centre next to a tertiary centre.



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# Limitations