Asymmetric Catalysis for Fine Chemical Synthesis

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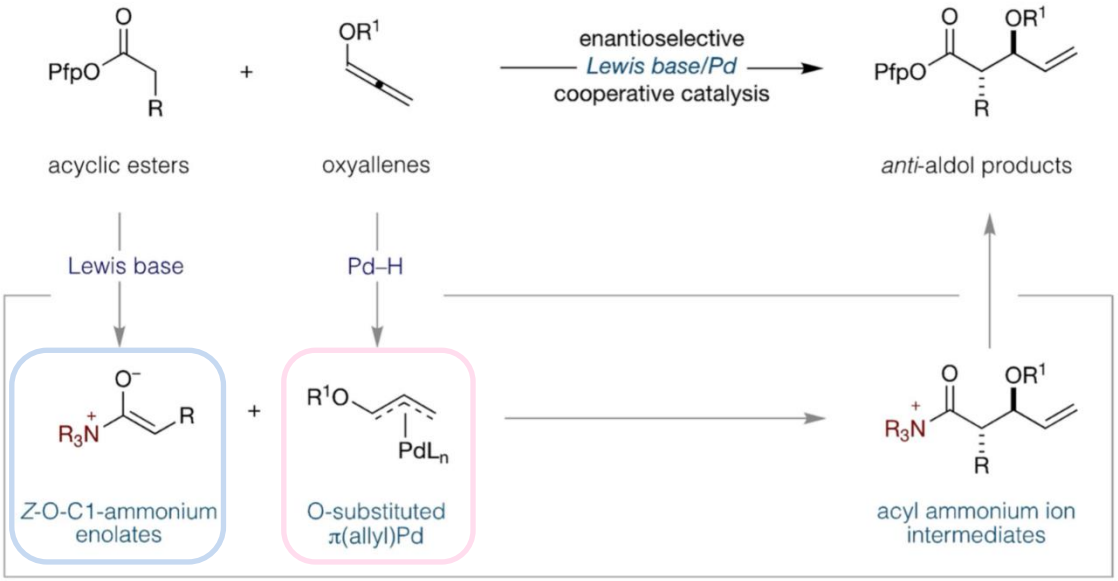
A Pd−H/Isothiourea Cooperative Catalysis Approach to *anti*-Aldol Motifs: Enantioselective α-Alkylation of Esters with Oxyallenes

Hua-Chen Lin, Gary J. Knox, Colin M. Pearson, Chao Yang, Veronica Carta, Thomas N. Snaddon

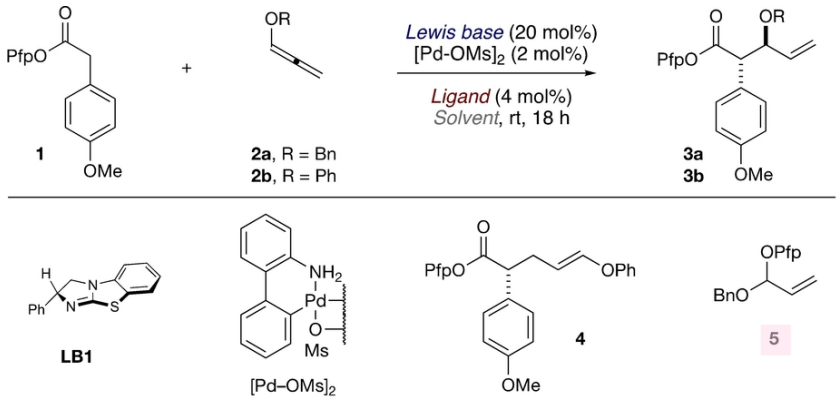
Introduction: Reaction and Reactivity

Enantioselective α-Alkylation of Esters with Oxyallenes



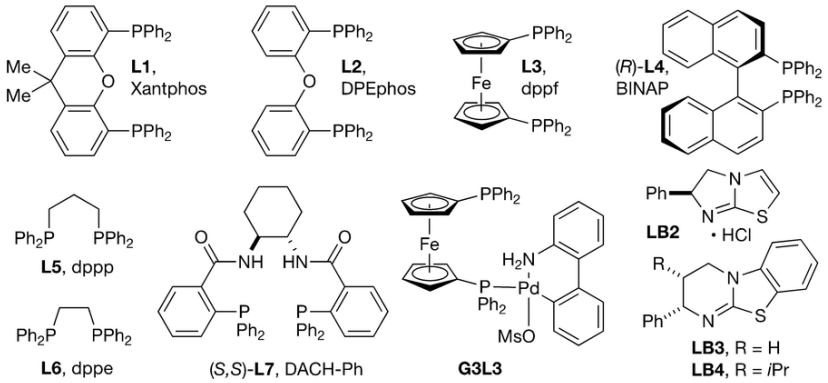
- **Reaction type**: Pd−H/isothiourea dual-catalysed coupling reaction.
- **Nucleophile**: activated acyclic esters.
- **Electrophile**: activated oxyallenes.
- **Product type**: enantioenriched anti-aldol motifs.
- **Principle of activation**:
  - **Isothiourea** Lewis base activates acyclic esters as **ammonium enolates**.
  - *In-situ* generated **Pd–H** activates oxyallenes as **π-allyl Pd** complexes.

Reaction Optimisation

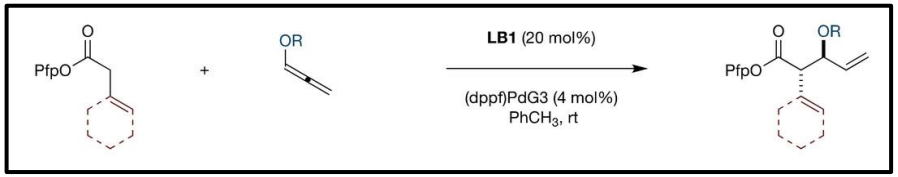


Entry[a]	oxyallene	*Lewis base*	*Ligand (bite angle)*	*Solvent*	Yield **3** [%][b]	dr[c]	*ee* [%][d]
1	**2a**	**LB1**	**L1** (108°)	THF	80 (13)	2.5:1	94
2				Et_2O	70 (16)	2.3:1	81
3				1,4-dioxane	53 (9)	2.3:1	96
4				$PhCH_3$	87 (4)	2.5:1	96
5				CH_2Cl_2	77 (13)	1.2:1	48
6				MeCN	79 (11)	1.1:1	30
7			**L2** (104°)	$PhCH_3$	86 (7)	3.2:1	97
8			**L3** (99°)		86 (6)	3.6:1	96
9			*(R)*- or *(S)*-**L4** (93°)		--	--	--
10			**L5** (91°)		--	--	--
11			**L6** (86°)		--	--	--
12			*(R,R)*- or *(S,S)*-**L7**		--	--	--
13			**G3L3**		86 (6)	3.6:1	96
14[e]		**LB2**			21 (13)	2.0:1	–85
15		**LB3**			83 (15)	3.4:1	88
16		**LB4**			87 (8)	1.3:1	20
17	**2b**	**LB1**			90	9.5:1	99

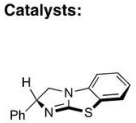
- Toluene was found to be the optimal solvent as side reactions (e.g. formation of hemiacetal byproduct **5**) were minimized.
- The bite angle of dppf (**L3**) at 99° was found to be optimal for the induction of diastereoselectivity.
- (+)-Benzotetramisole (**LB1**) was the most effective Lewis base catalyst.
- Final conditions: **G3L3** (4 mol%) + **LB1** (20 mol%) in toluene.



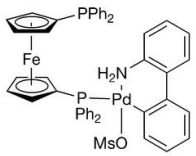
Scope and Selectivity



Catalysts:

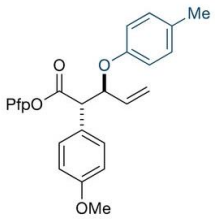


LB1

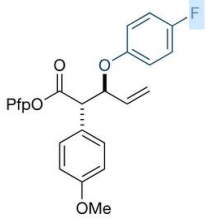


(dppf)PdG3 (**G3L3**)

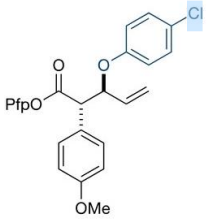
Electrophile Scope



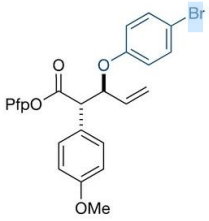
6, 83%
5.8:1 dr, 99% ee



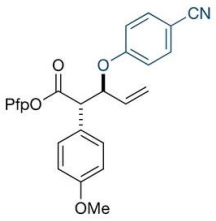
7, 91%
6.3:1 dr, 99% ee



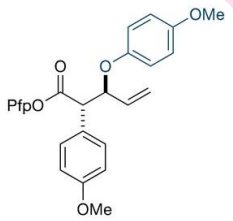
8, 90%
5.5:1 dr, >99% ee



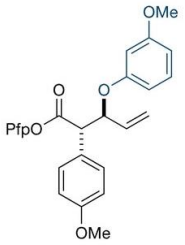
9, 81%
5.5:1 dr, 96% ee



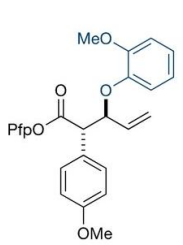
10, 51%
2.9:1 dr, 99% ee



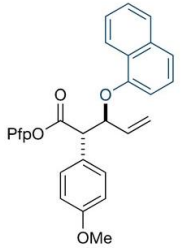
11, 92%
5.4:1 dr, 99% ee



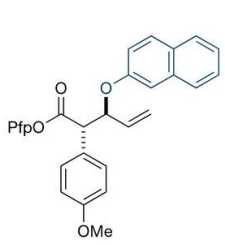
12, 81%
6.8:1 dr, 98% ee



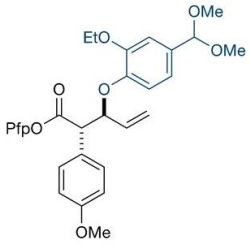
13, 80%
6.0:1 dr, 95% ee



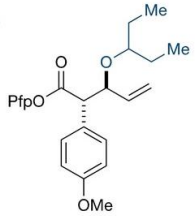
14, 84%
4.7:1 dr, 99% ee



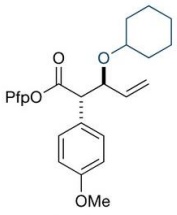
15, 79%
3.2:1 dr, 99% ee



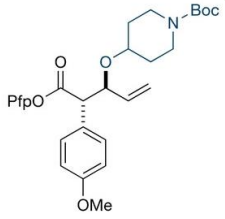
16, 90%
4.2:1 dr, 98% ee



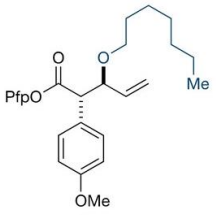
17, 84%
2.4:1 dr, 99% ee (NH_2)



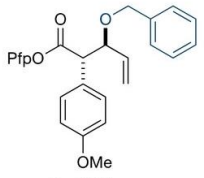
18, 90%
1.7:1 dr, 97% ee



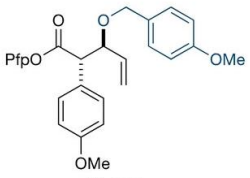
19, 81%
1.2:1 dr, 99% ee



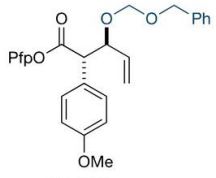
20, 88%
3.3:1 dr, 97% ee



3a, 85%
5.4:1 dr, 99% ee
Bn-protected



21, 81%
2.9:1 dr, 99% ee
PMB-protected



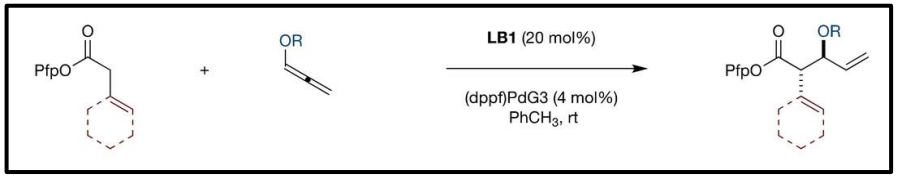
22, 80%
6.0:1 dr, >99% ee
BOM-protected

E⁺ scope: tolerates **aryloxy** and **alkoxy** allenes possessing halogens, EDGs, and Boc-protected amines.

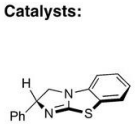
Yield: very high (up to 92%); excellent enantio-selectivity (up to >99% ee).

Diastereoselectivity depends on the *O*-substituent of the allene (e.g. 9.5:1 dr with phenoxyallene).

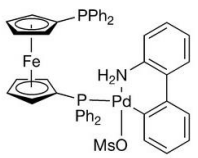
Scope and Selectivity



Catalysts:

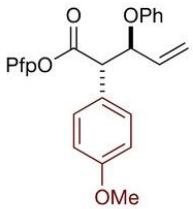


LB1

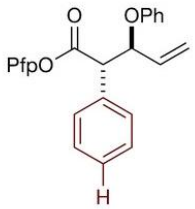


(dppf)PdG3 (**G3L3**)

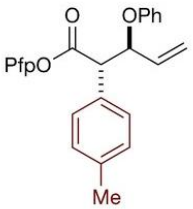
Nucleophile Scope



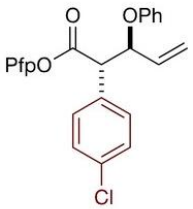
3b, 90%
9.5:1 dr, 99% ee



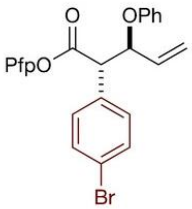
23, 90%
8.0:1 dr, 99% ee



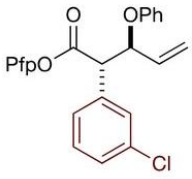
24, 82%
8.5:1 dr, 99% ee



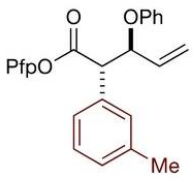
25, 81%
7.7:1 dr, >99% ee



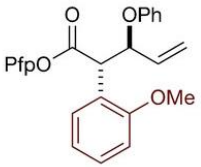
26, 76%
7.3:1 dr, 99% ee



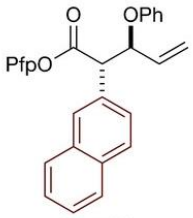
27, 80%
8.1:1 dr, 99% ee



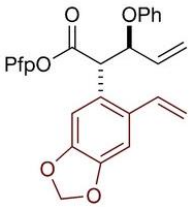
28, 82%
8.1:1 dr, 99% ee



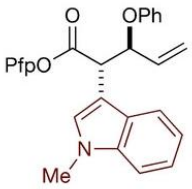
29, 68%
5.5:1 dr, 99% ee



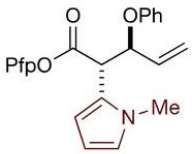
30, 81%
7.0:1 dr, 98% ee



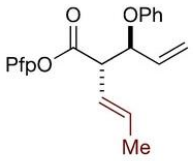
31, 64%
3.4:1 dr, 98% ee



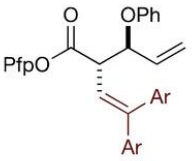
32, 75%
13.6:1 dr, >99% ee



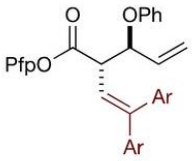
33, 52%
3.3:1 dr, 90% ee



34, 71%
6.1:1 dr, 99% ee



Ar = (4-F)C_6H_4
35, 72%
1.9:1 dr, 99% ee

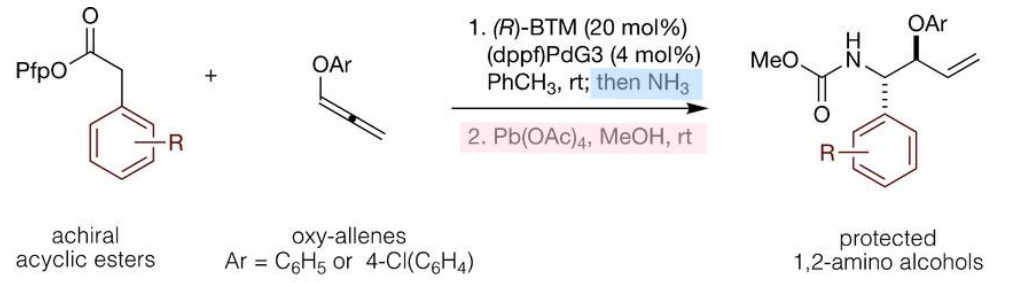


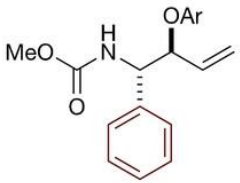
Ar = (4-OMe)C_6H_4
36, 86%
1.8:1 dr, 99% ee

Nu scope: tolerates (hetero)aryl-, alkenyl-substituted Pfp esters.

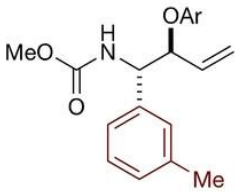
Yield: very high (up to 90%) but lower for electron-rich arenes and heteroaromatics.

Product Conversion to 1,2-Amino Alcohols

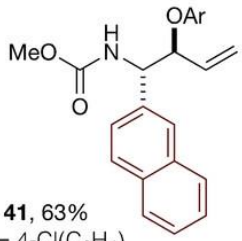




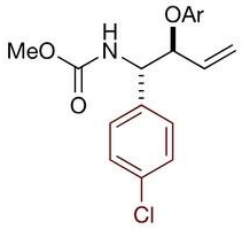
39, 65%, Ar = 4-Cl(C_6H_4)
>20:1 dr, >99% ee



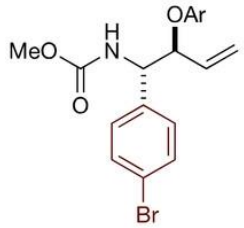
40, 62%, Ar = C_6H_5
>20:1 dr, >99% ee



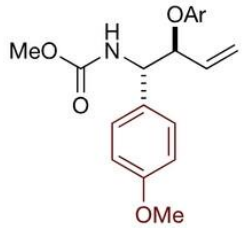
41, 63%
Ar = 4-Cl(C_6H_4)
>20:1 dr, >99% ee



42, 60%, Ar = 4-Cl(C_6H_4)
>20:1 dr, >99% ee



43, 64%, Ar = C_6H_5
>20:1 dr, >99% ee



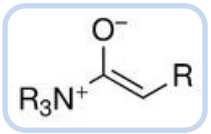
44, 69%, Ar = C_6H_5
>20:1 dr, >99% ee

- Pfp ester products react with NH_3 to form the corresponding **primary amides**.
- Subsequent **Hofmann rearrangement** under oxidative conditions yields *N*-carbamoyl-1,2-amino alcohols.
- Highlights **synthetic utility** and **robustness** of the dual-catalytic system.

Deuterium Tracking Experiment

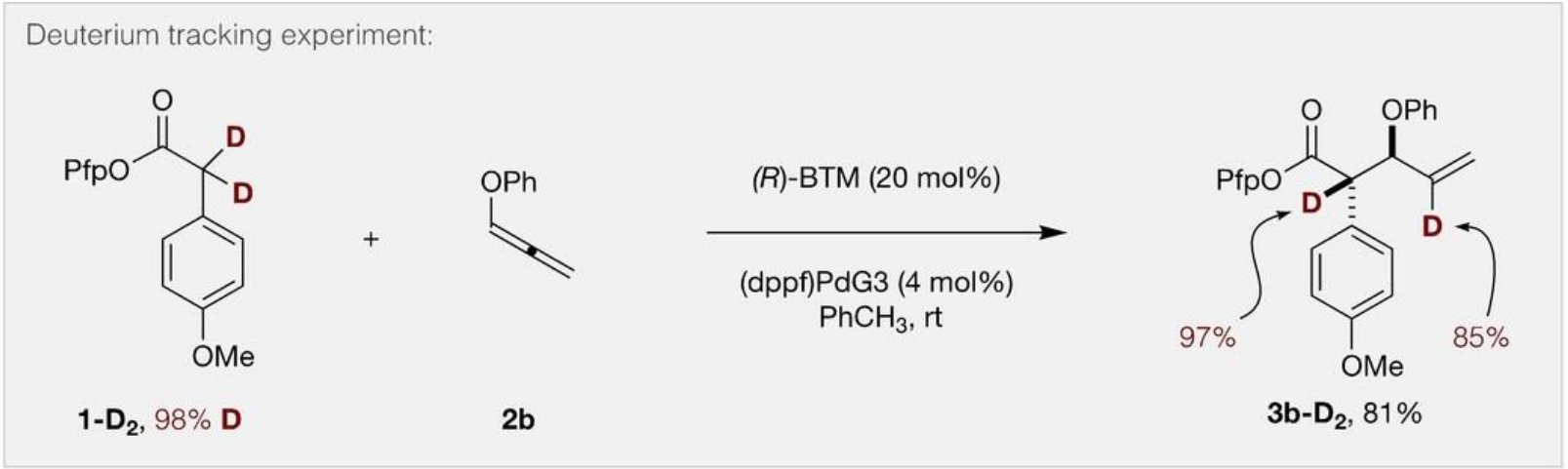
Observations:

- No exogenous **base** required to generate **ammonium enolate**.



- No exogenous **Brønsted acid** required to generate **Pd-H intermediate**.

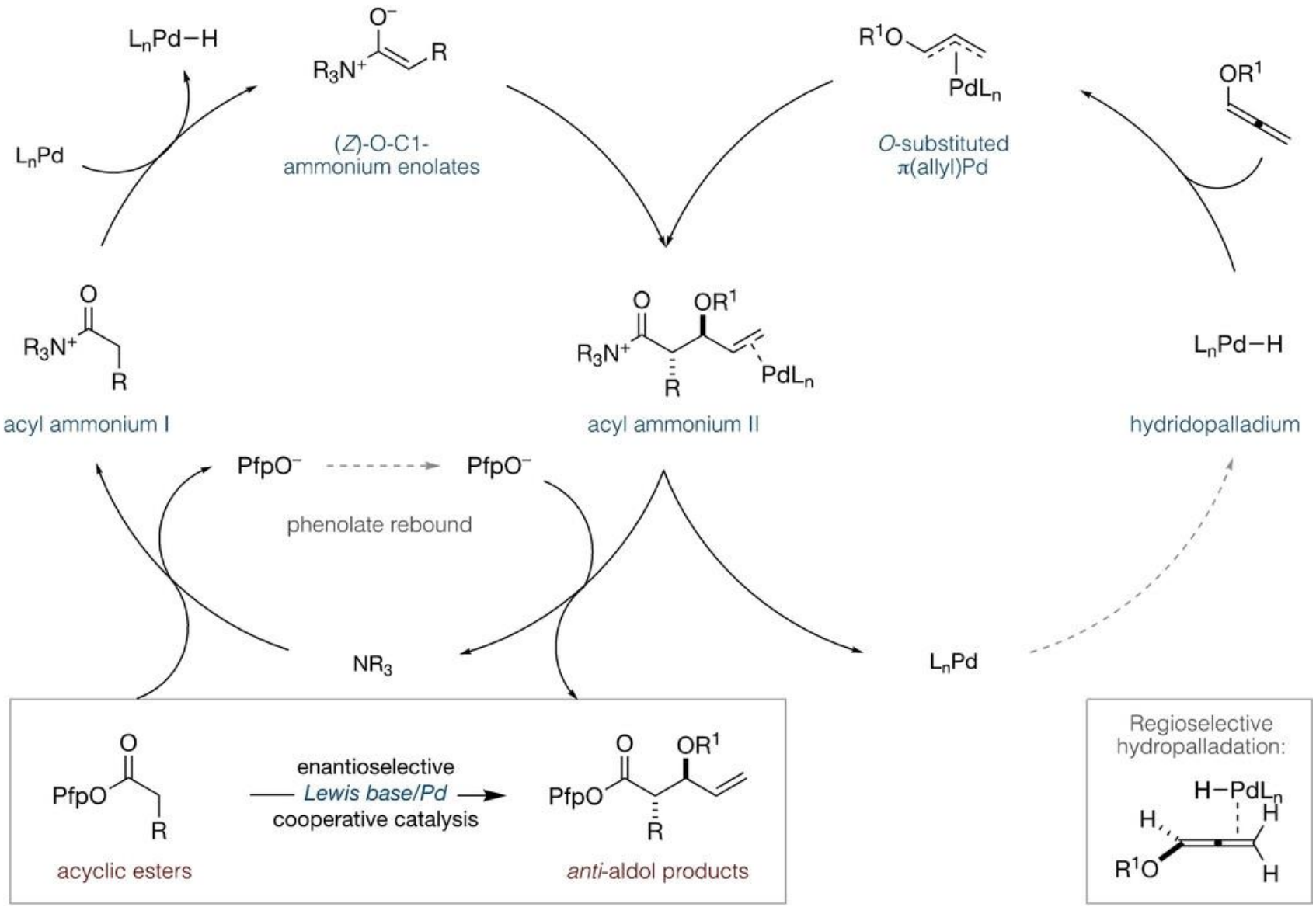
L_nPd-H



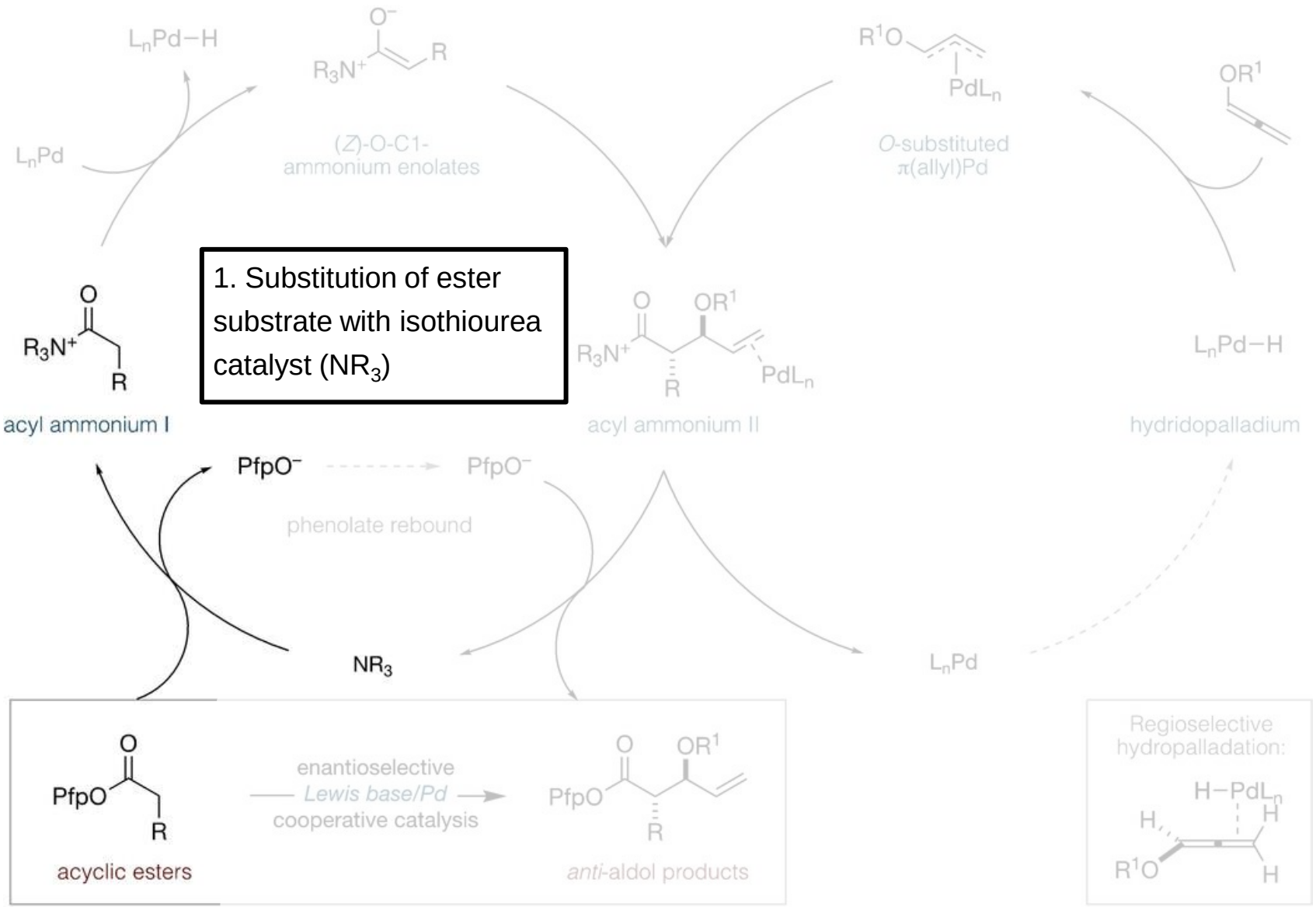
Reaction with deuterium-enriched substrate **1-D_2** shows:

- One D atom incorporated at **central carbon** of oxyallene.
- The other D atom is **retained**.

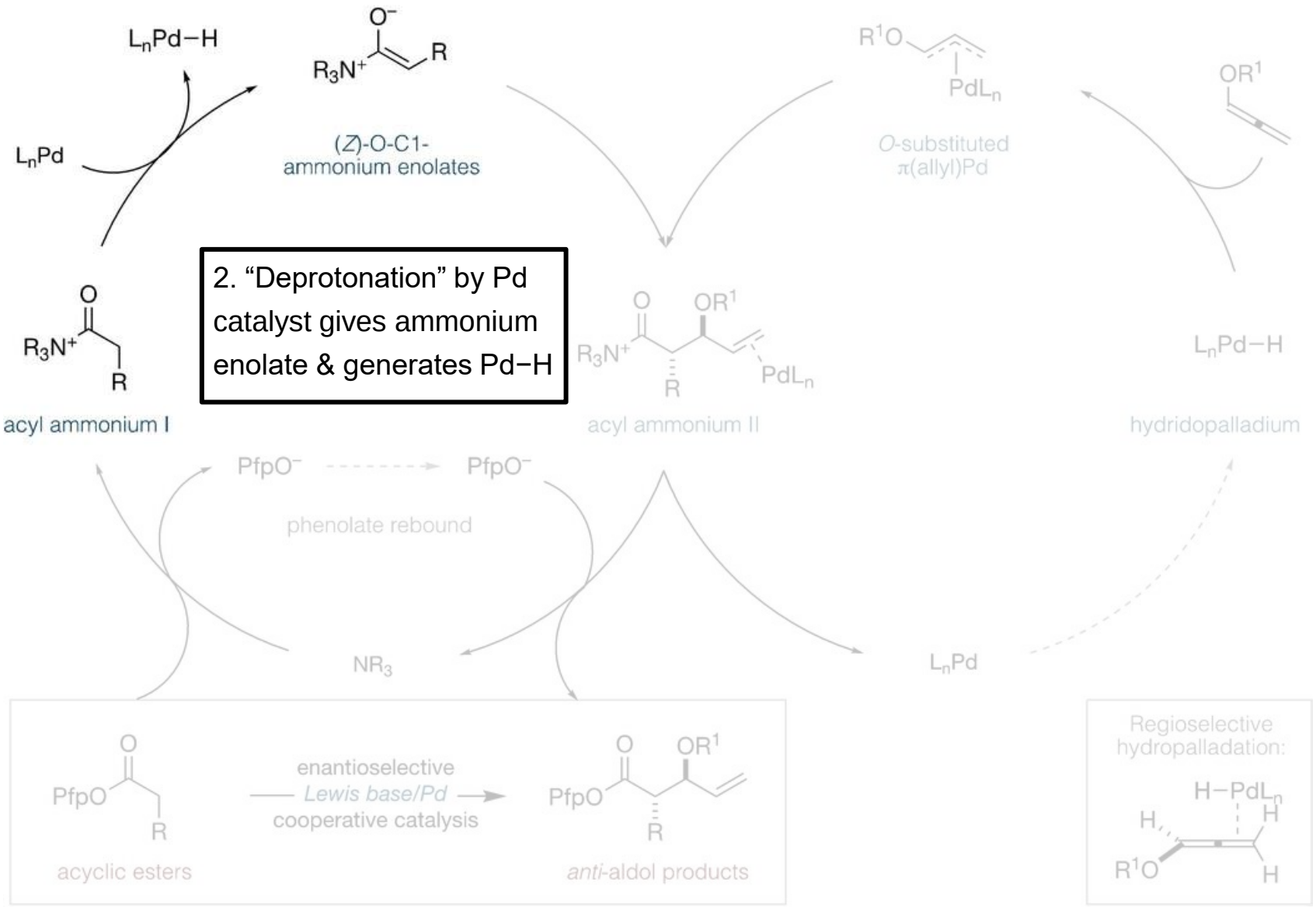
Proposed Mechanism



Proposed Mechanism

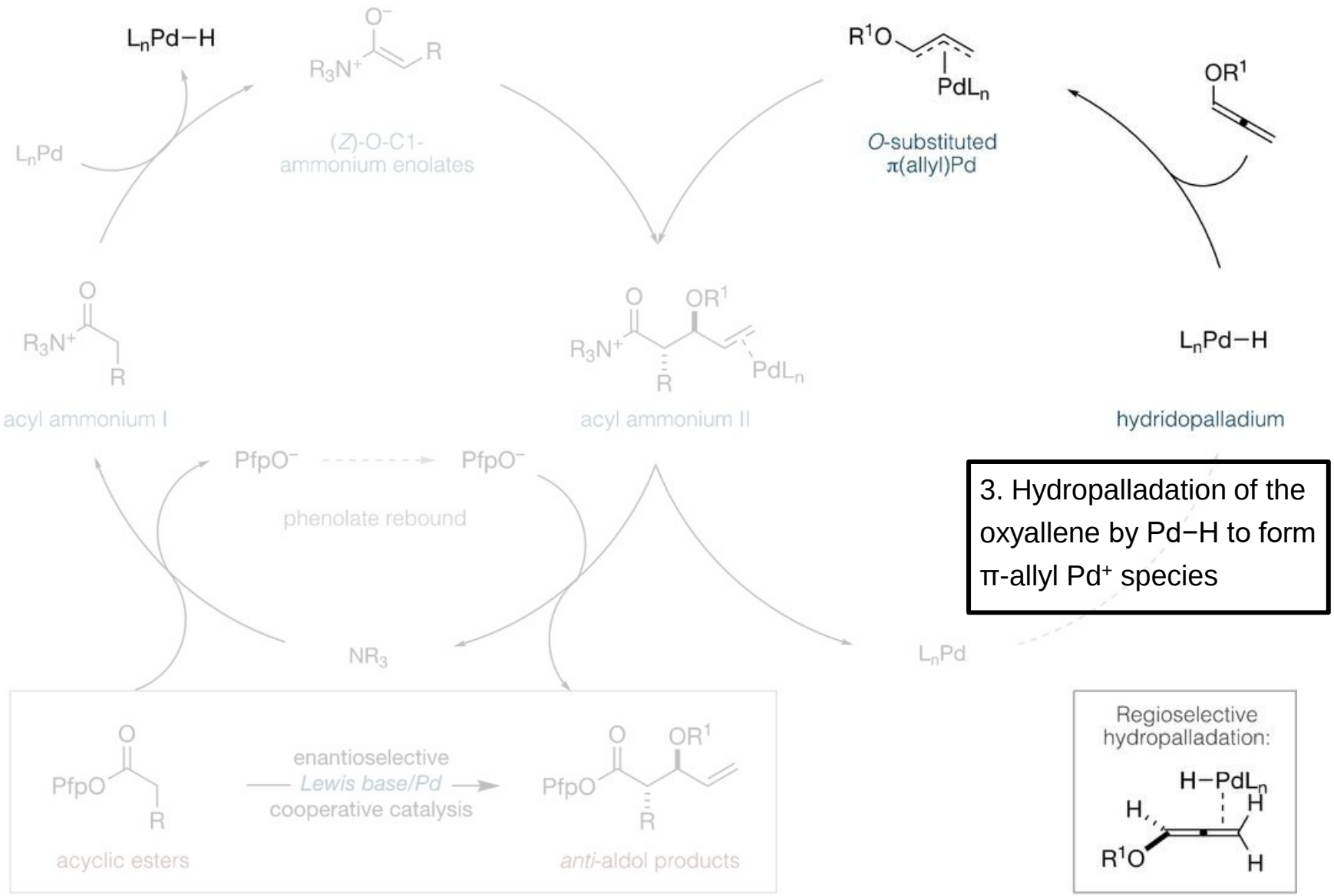


Proposed Mechanism



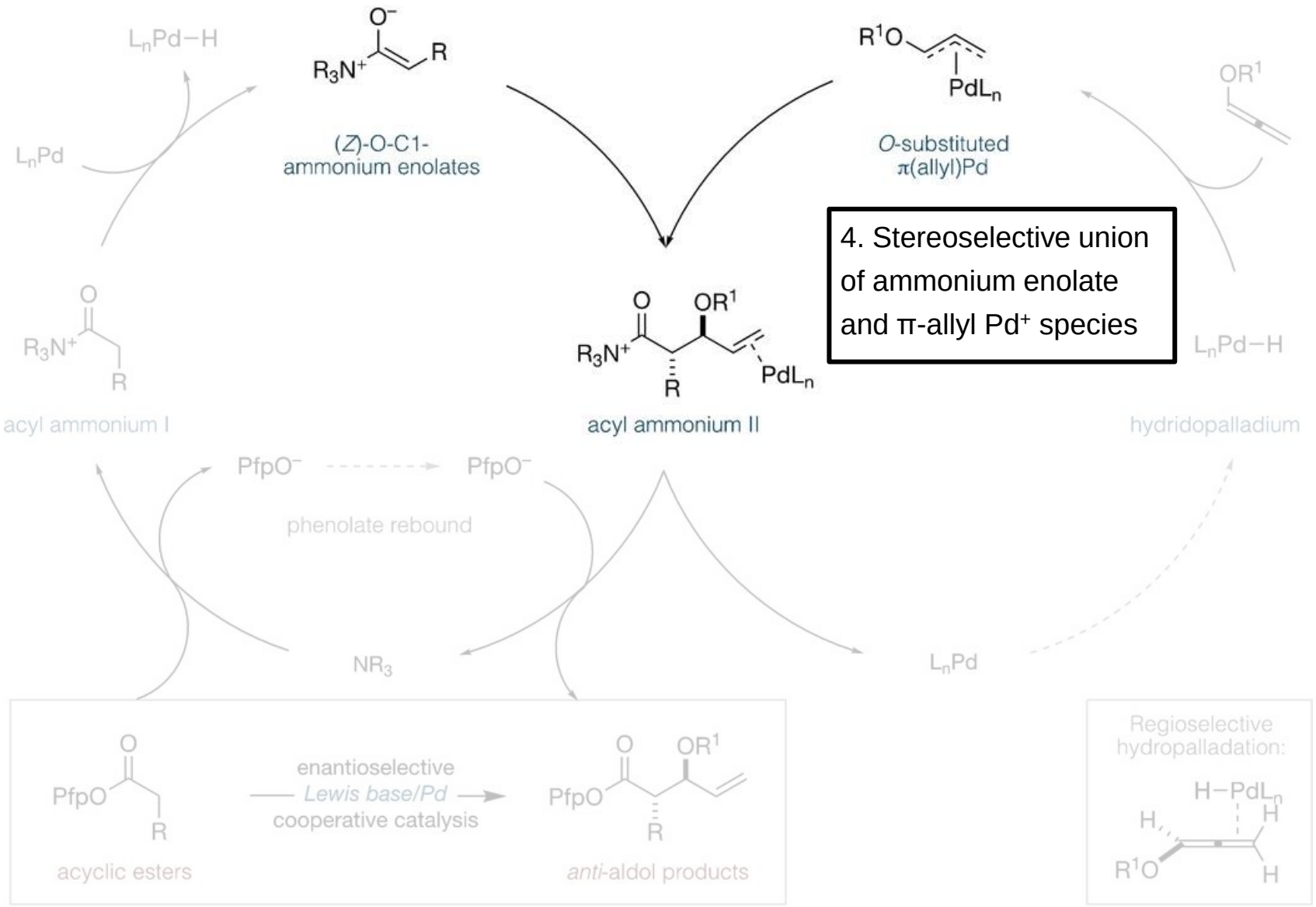
2. “Deprotonation” by Pd catalyst gives ammonium enolate & generates Pd–H

Proposed Mechanism

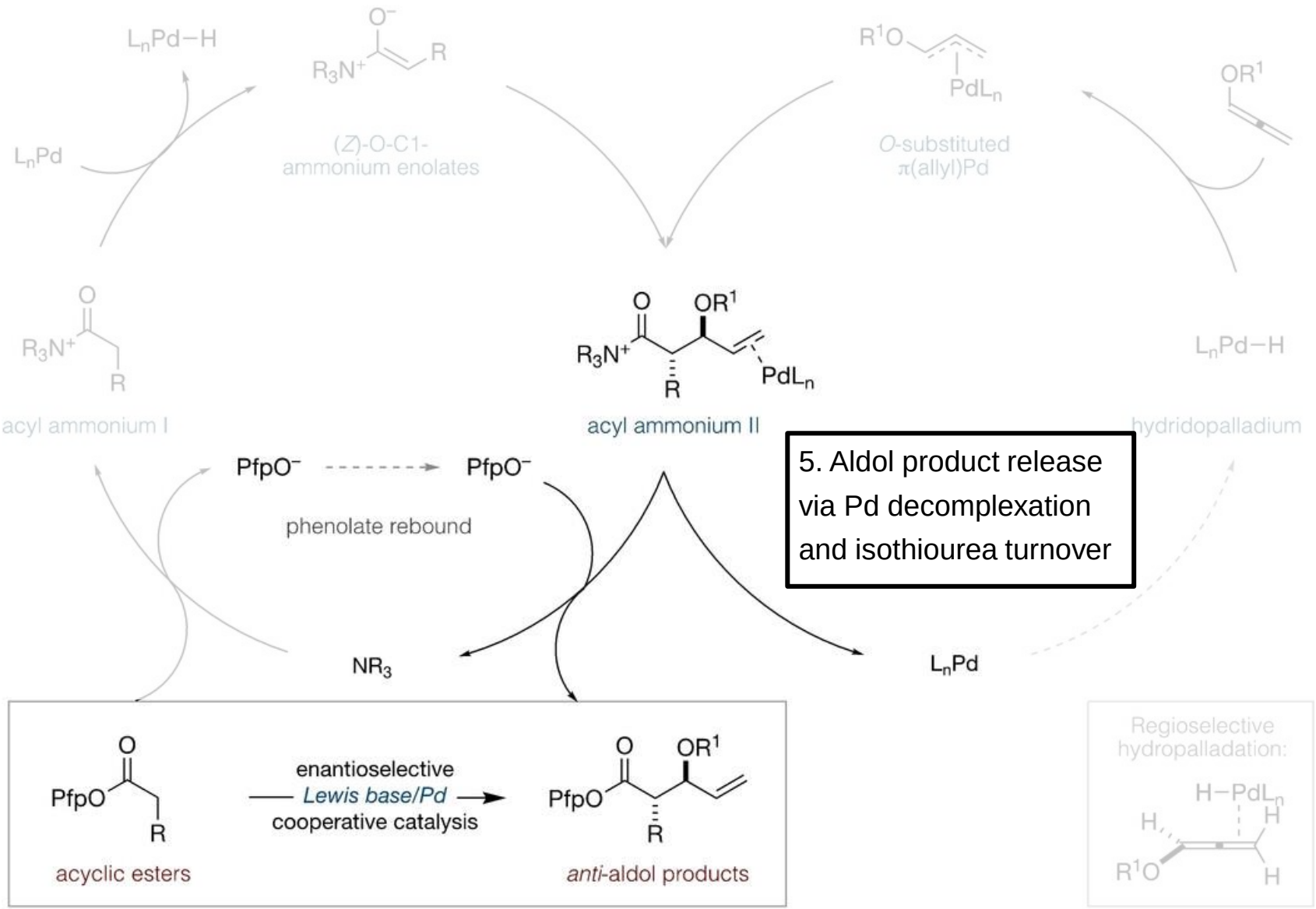


3. Hydropalladation of the oxyallene by Pd−H to form π-allyl Pd^+ species

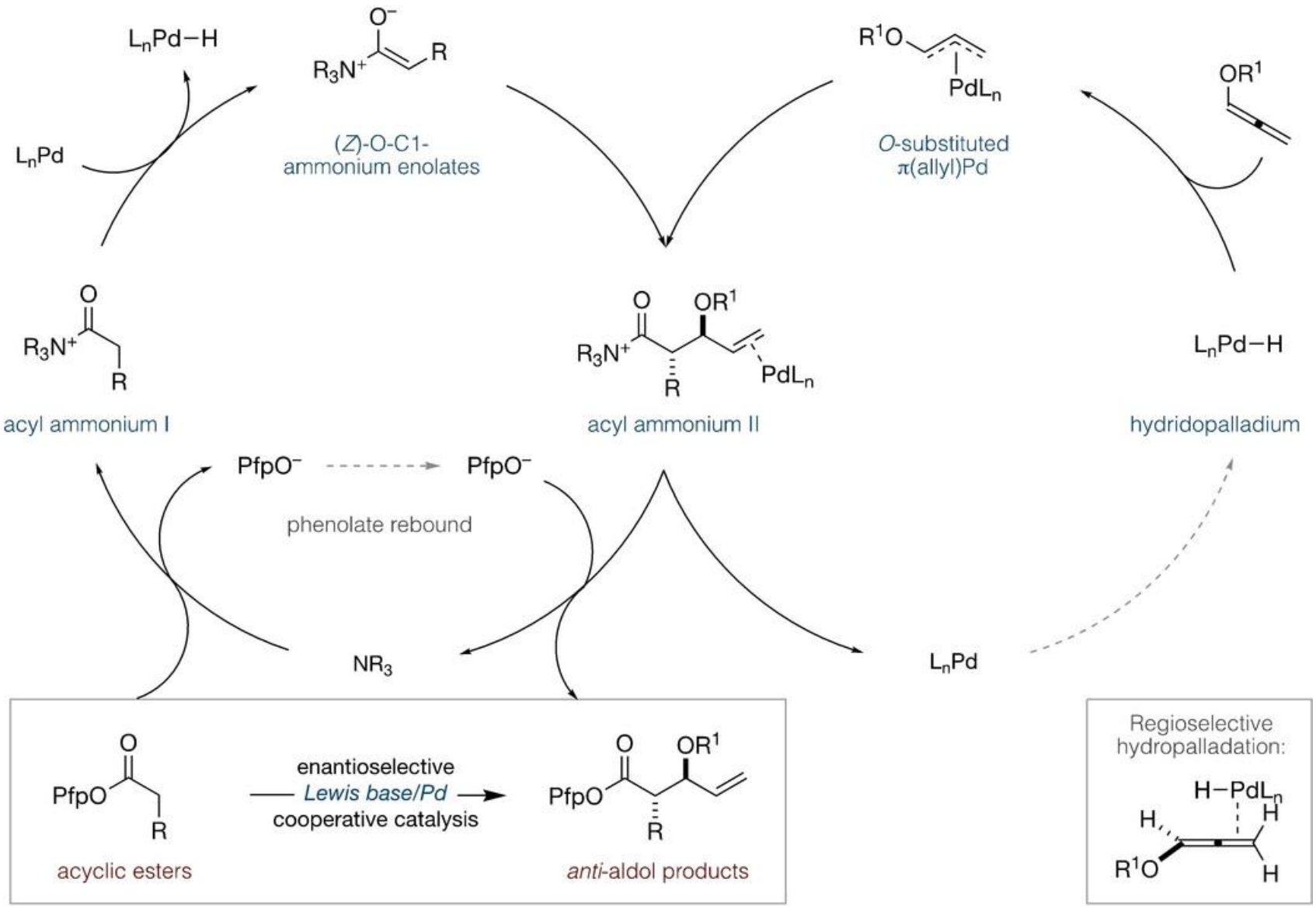
Proposed Mechanism



Proposed Mechanism



Proposed Mechanism



Critical Analysis: Novelty

Strong points

- **Direct** construction of anti-aldol products, with stereoselectivity regulated at the **catalyst level** – complementary to aldol methodologies with **reagent-level** asymmetric induction.
- ***O*-substituted aldol products** here are otherwise challenging to access due to competing retro-Aldol fragmentation.

Weaker points

- (Stereoselecitve) Aldol reactions are well-established, with many (dual-catalytic) protocols to generate each isomer in a **stereodivergent** manner.
- **Pd/isothiourea relay catalysis** also well-known, previous reports (Snaddon, Smith) have already described stereoselective α-alkylation of esters with Pd π-allyl complexes.
    - Though, the generation of *O*-substituted Pd π-allyl complexes from oxyallenes is novel.

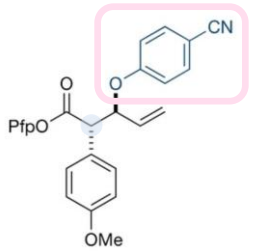
Critical Analysis: Practicability

Strong points

- Convenient reaction set-up (“dump-and-stir”).
- Excellent **enantioselectivity** and good **diastereoselectivity**.
- Both isothiourea and Pd catalysts are **commercially-available**.
- Pfp ester & aryloxy group in product act as handles for subsequent orthogonal modifications.
- Oxyallene substrates typically prepared in one step from respective terminal alkyne.

Weaker points

- **Pfp-ester required**, limiting nucleophile scope
- sp^2 centre required at β-position of Pfp-ester
- Electron-poor *O*-substituent on oxyallene less well-tolerated
- **Terminal allene** required, limiting substitution pattern of aldol product



10, 51%
2.9:1 dr, 99% ee

Critical Analysis: Sustainability

Strong points

- Mild conditions (r.t.).
- Low Pd catalyst loading (4 mol%).
- Solvent is OK (toluene classified as «yellow» solvent).
- 100% atom economy.

Weaker points

- High organocatalyst loading (20 mol%).
- Pd is a precious metal, rare and expensive.

Questions

Question 1

The regioselectivity of Pd allylations is traditionally in favour of linear over branched products, the latter typically obtained with other metals like Ir. Why this reaction leads to branched products?

Question 2

Explain the low diastereoselectivity of the reaction in terms of facial selectivity, which stereocenter of the product is poorly controlled and what is the mechanism of the enolate addition to the Pd allyl intermediate.

Question 3

What are the peculiarities of the ammonium enolate formed with this isothiourea Lewis base catalyst compared to the chiral enolates that you have seen previously?