Asymmetric Catalysis for Fine Chemical Synthesis

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Lilian Bourqui & William Pellassy

Science

Dynamic kinetic asymmetric arylation and alkenylation of ketones

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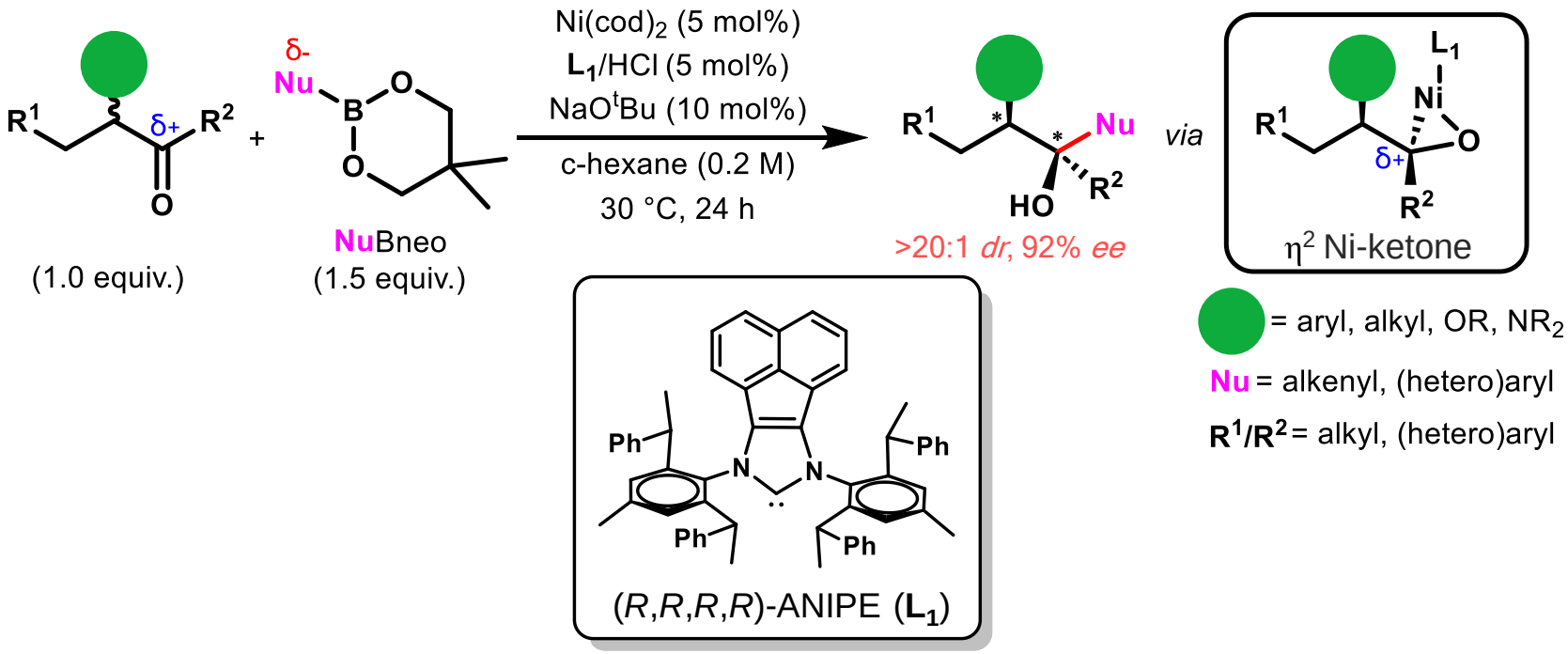
Introduction: Reaction and Reactivity

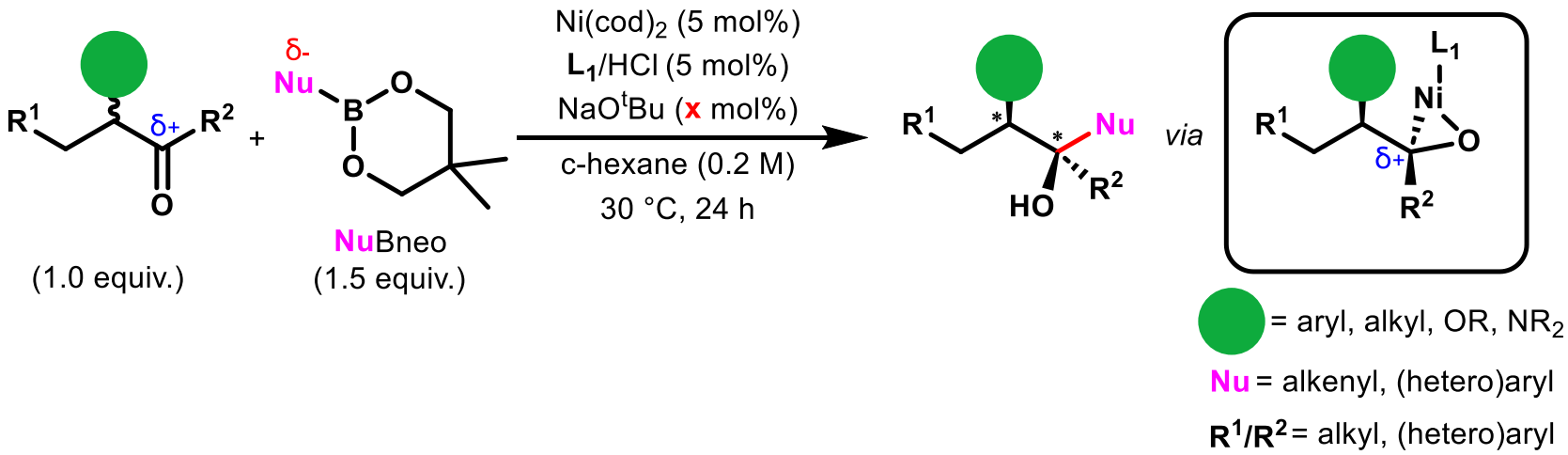
Enantioconvergent addition to ketones



- **Reaction Type:** Ni-catalyzed enantioconvergent addition of aryl- and alkenyl-boronate esters to racemic ketones.
- **« Electrophile »:** Carbon in η^2 Ni-ketone complex
- **Nucleophile:** Activated Aryl- or alkenyl-boronate esters
- **Product Type:** Enantioenriched tertiary alcohols with adjacent stereocenter
- **Catalyst:** Ni(II) complexed with chiral NHC (**L_1**)

Reaction Optimization

Optimal conditions

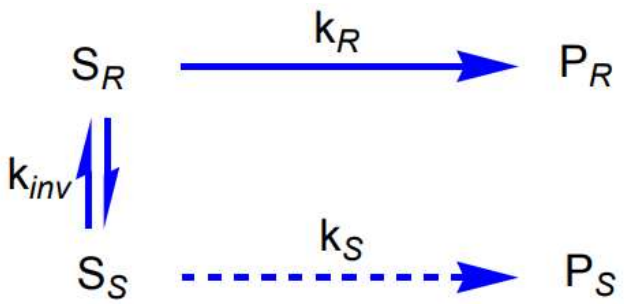


Entry	Ligand	Solvent	Base (mol%)	Yield (%)†	ee (%)‡	dr†
15	**L1/HCl**	cyclohexane	NaO^tBu (300)	<2	ND	ND
16	**L1/HCl**	cyclohexane	NaO^tBu (150)	45	91	>20:1
17	**L1/HCl**	cyclohexane	NaO^tBu (100)	62	91	>20:1
18	**L1/HCl**	cyclohexane	NaO^tBu (60)	93	92	>20:1
19	**L1/HCl**	cyclohexane	NaO^tBu (10)	99	92	>20:1
20	**L1**	cyclohexane	NaO^tBu (0)	90	92	>20:1

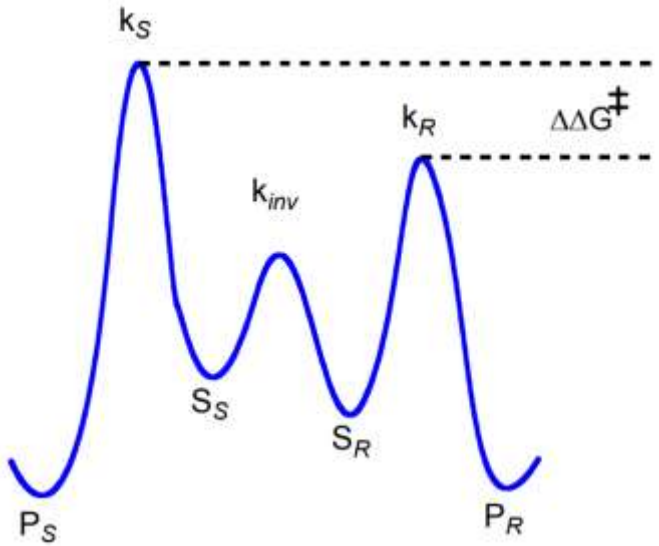
- NaO^tBu was found to be the optimal base for in situ deprotonation of imidazolium chloride
- The proportion of base was found to significantly impact the yield

Dynamic Asymmetric Kinetic Transformation

Dynamic Kinetic Resolution (DKR)



Curtin-Hammett Principle:

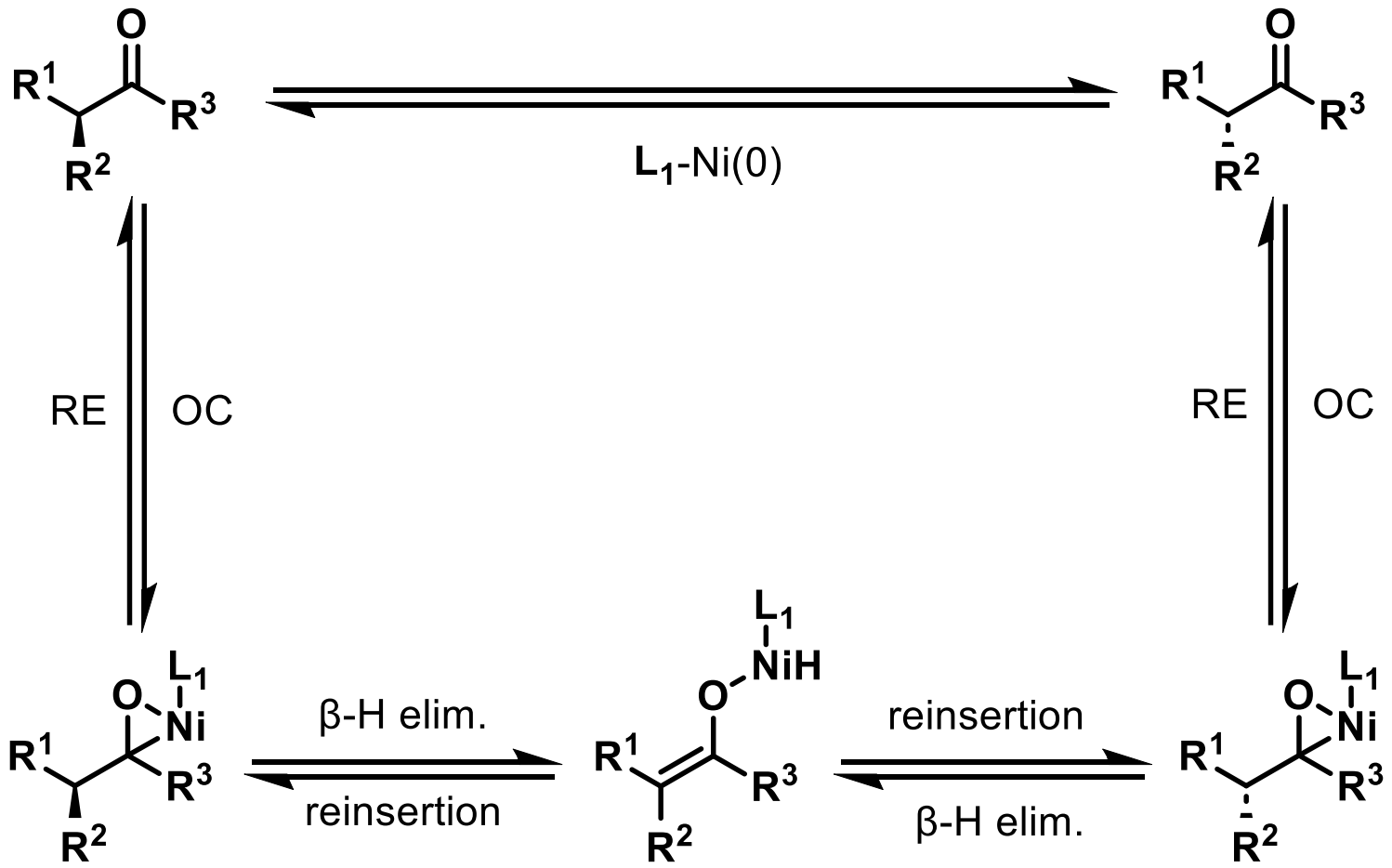


- **Dynamic kinetic resolution:** $k_{inv} >> k_R >> k_S$
- **Kinetic control:** **Interconversion** and **free energies** of the **transition states**
- DKR enables combination of **racemization** with **enantioselective transformations**

Pellissier, H. *Tetrahedron*, **2003**, 59, 8291.

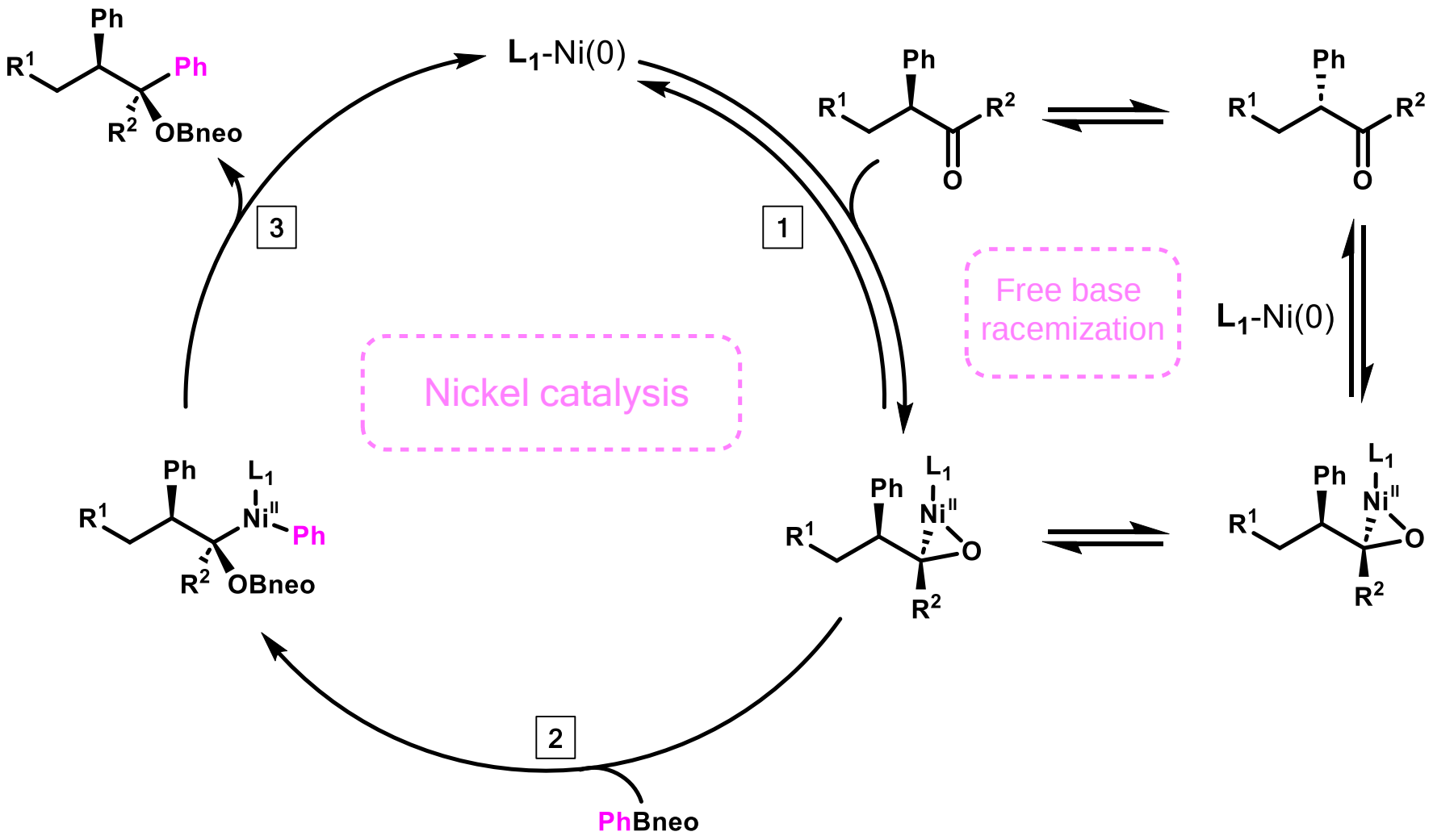
Dynamic Asymmetric Kinetic Transformation

Base free racemization of non-activated ketones



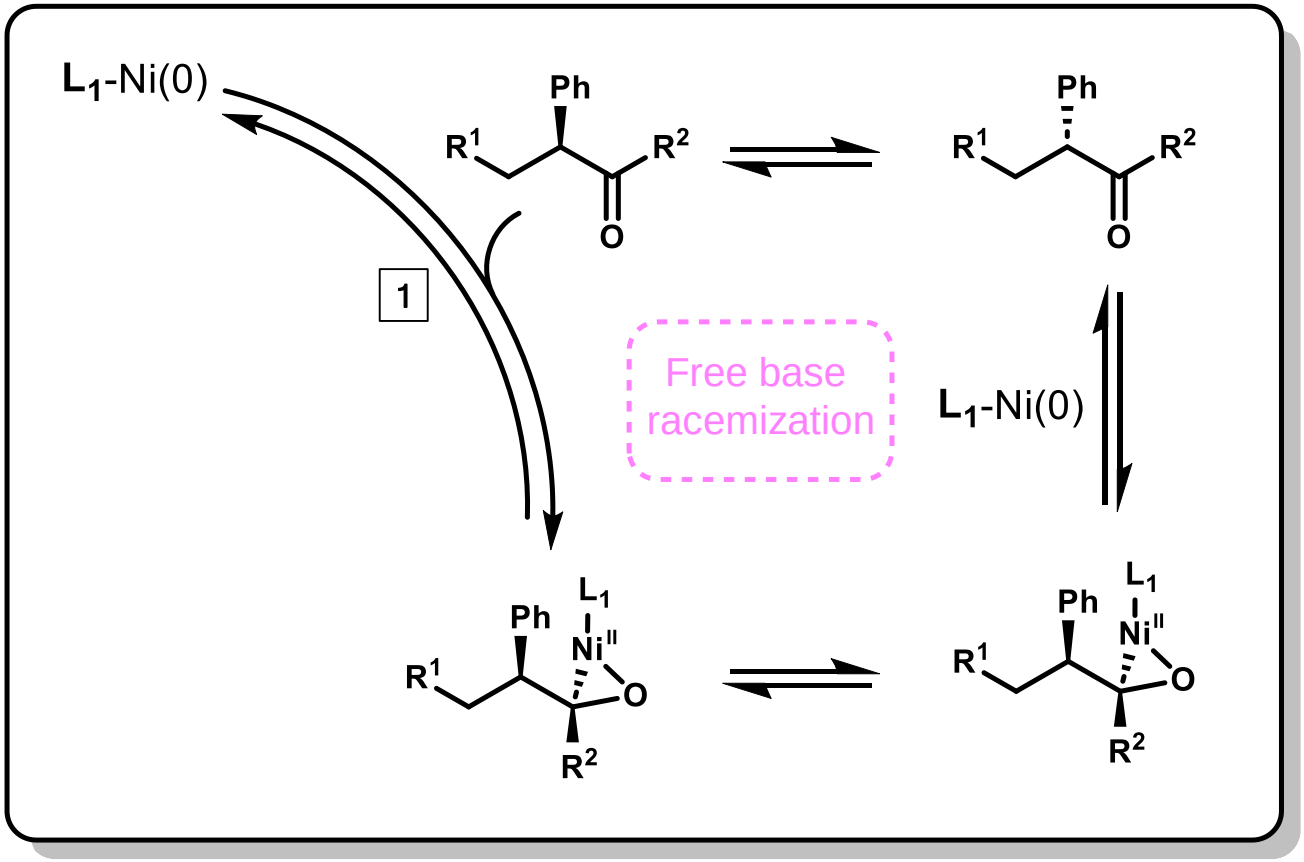
Pellissier, H. *Tetrahedron*, **2003**, 59, 8291.

Catalytic Cycle



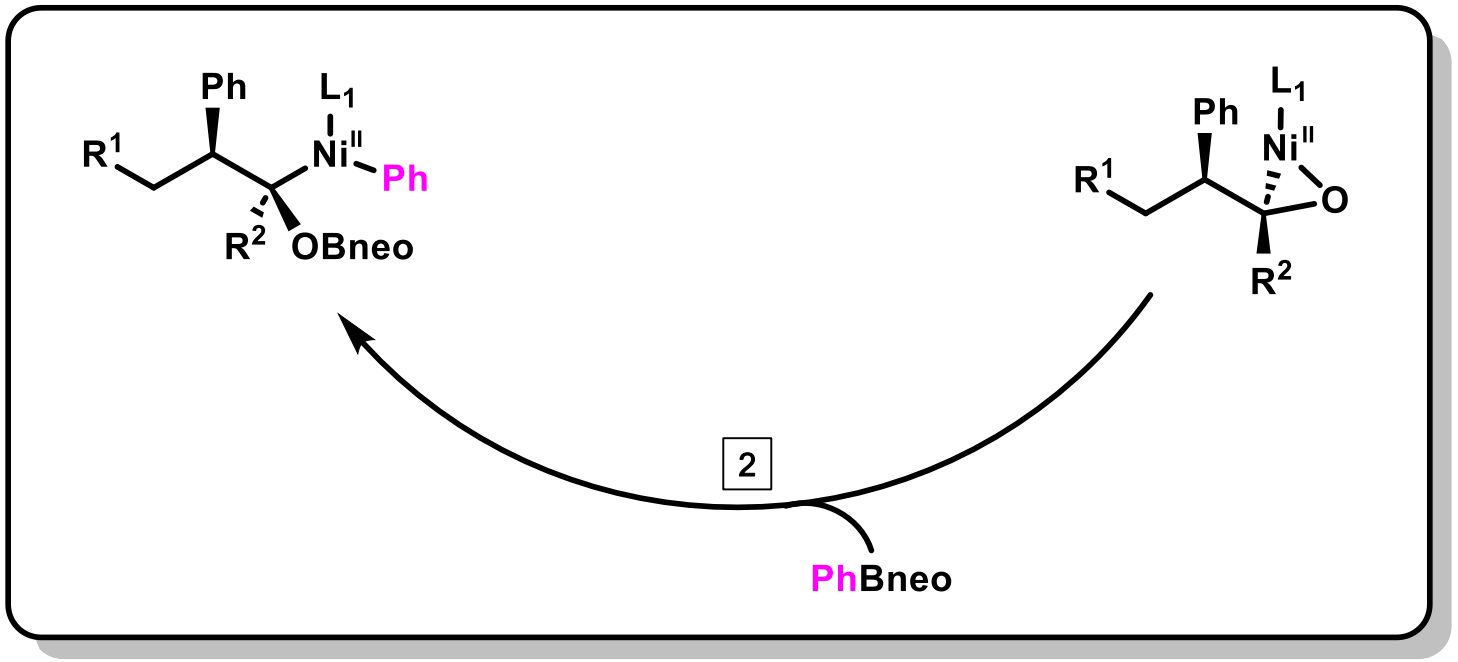
Catalytic Cycle 1

Oxydative cyclization



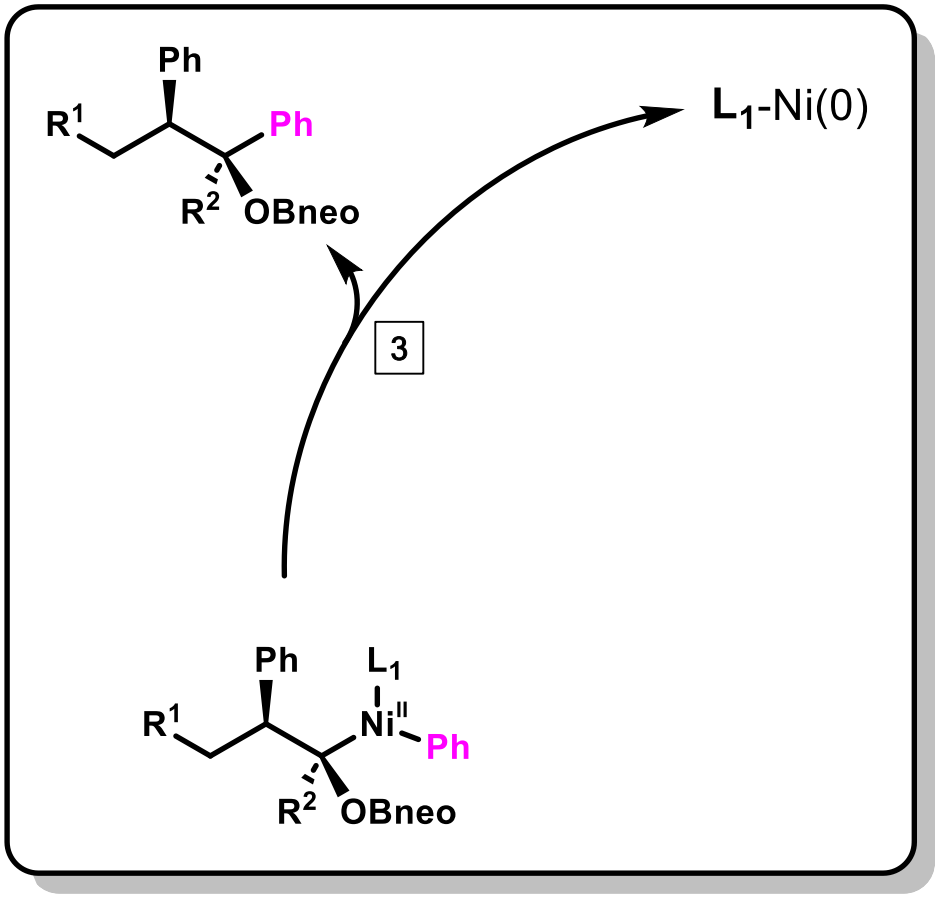
Catalytic Cycle 2

Transmetallation



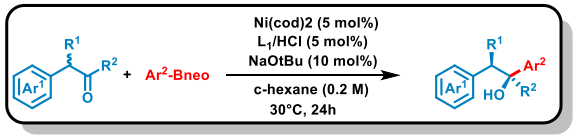
Catalytic Cycle 3

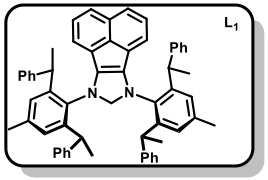
Reductive elimination



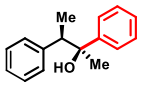
Scope

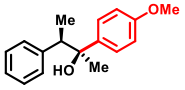
Arylation of α-aryl ketones

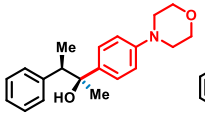


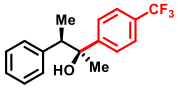


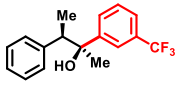
(Hetero)aryl Boronates

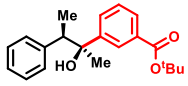

3a, 97%, 92% ee

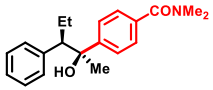

3c, 92%, 92% ee

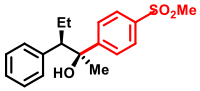

3e, 91%, 93% ee

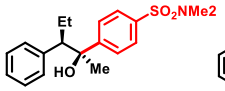

3i, 91%, 93% ee

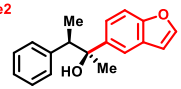

3j, 65%, 88% ee

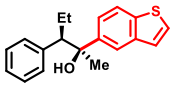

3m, 83%, 87% ee

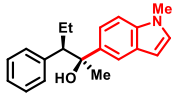

3n, 95%, 96% ee

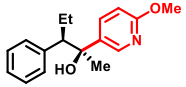

3o, 96%, 95% ee


3p, 68%, 96% ee

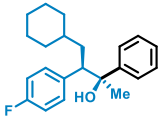

3q, 90%, 90% ee

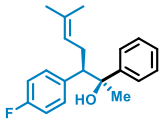

3r, 65%, 94% ee

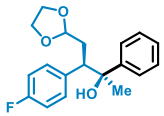

3s, 88%, 95% ee

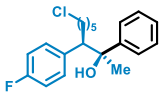

3u, 45%, 91% ee

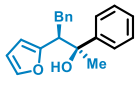
Alkyl-Alkyl Ketones

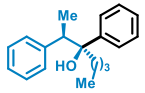

3x, 83%, 94% ee


4a, 78%, 86% ee

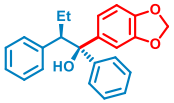

4b, 96%, 95% ee

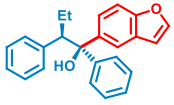

4d, 99%, 98% ee

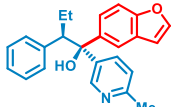

4f, 93%, 89% ee


4h, 65%, 80% ee
8:1 dr

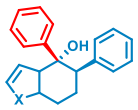
Aryl-Alkyl Ketones

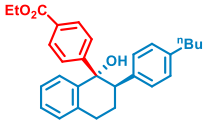

4j, 84%, 84% ee

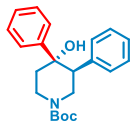

4l, 83%, 90% ee


4r, 50%, 86% ee

Cyclic Ketones


X = O, 4s, 68%, 97% ee
X = S, 4t, 71%, 91% ee

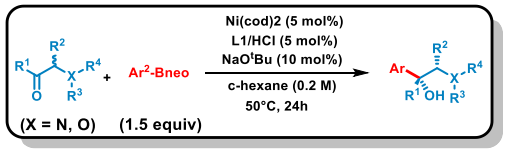

4u, 82%, 98% ee

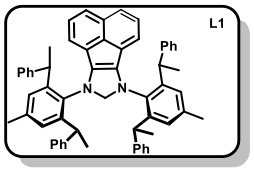

4x, 93%, 80% ee

- If not indicated, >20:1 dr
- High diastereoselectivity and enantioselectivity
- High yield
- Broad scope

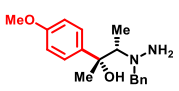
Scope

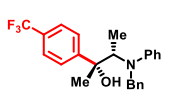
Scope of α-amino or α-oxy ketones

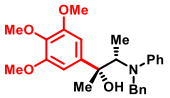


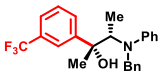


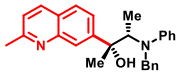
(Hetero)aryl Boronates

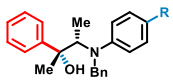

6c, 85%, 94% ee


6h, 88%, 96% ee

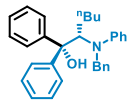

6f, 80%, 94% ee

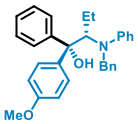

6i, 74%, 94% ee

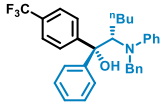

6s, 98%, 92% ee

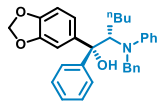

7k, R = OCF_3, 93%, 95% ee
7l, R = F, 88%, 94% ee
7m, R = ^{t}Bu, 86%, 93% ee
7j, R = CO_2Et, 80%, 95% ee

Aryl-Alkyl Ketones

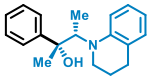

6v, 93%, 85% ee

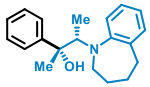

6x, 95%, 89% ee

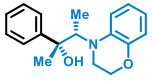

6y, 76%, 92% ee

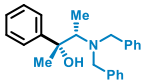

7a, 80%, 82% ee

Alkyl-Alkyl Ketones

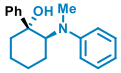

7g, 51%, 89% ee

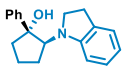

7h, 64%, 91% ee

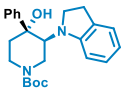

7n, 82%, 87% ee

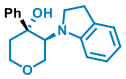

7o, 41%, 76% ee

Cyclic Ketones

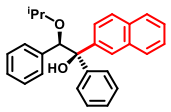

7b, 55%, 91% ee

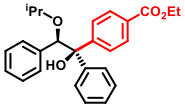

7c, 88%, 75% ee

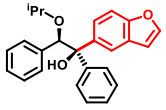

7d, 88%, 94% ee

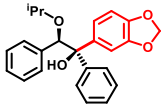

7e, 93%, 96% ee

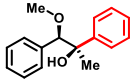
β-Alkokxy Tertiary Alcohols

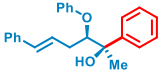

9a, 82%, 87% ee
9:1 dr


9b, 56%, 90% ee
7:1 dr


9c, 47%, 81% ee
6:1 dr

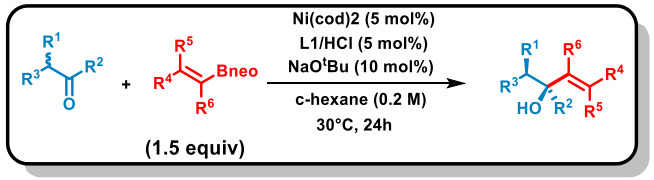

9d, 60%, 85% ee
6:1 dr

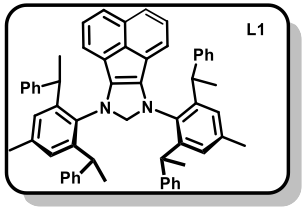

9e, 95%, 90% ee
6:1 dr


9f, 23%, 76% ee

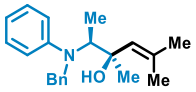
Scope

Scope of racemic ketones

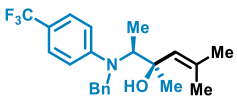




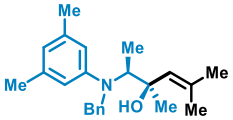
α-Amino Ketone Scope



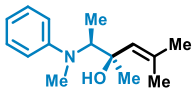
11a, 95%, 95% ee



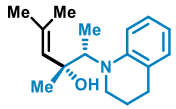
11d, 93%, 94% ee



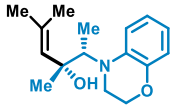
11e, 79%, 93% ee



11h, 70%, 89% ee

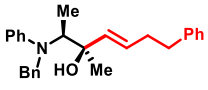


11d, 78%, 89% ee

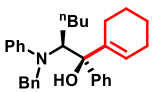


11j, 96%, 86% ee

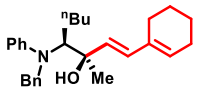
Vinyl boronate scope



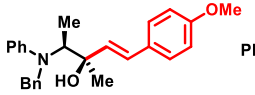
11k, 52%, 73% ee



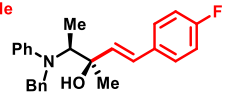
11m, 78%, 80% ee



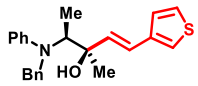
11o, 81%, 81% ee



11q, 42%, 81% ee

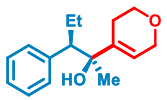


11r, 48%, 75% ee

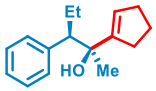


11s, 50%, 80% ee

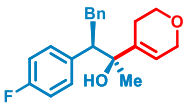
α-Aryl Ketone scope



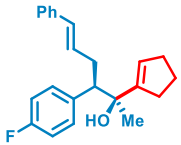
12a, 75%, 92% ee



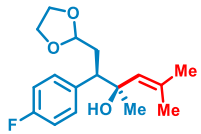
12c, 70%, 87% ee



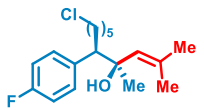
12e, 59%, 87% ee



12f, 45%, 95% ee



12g, 76%, 88% ee



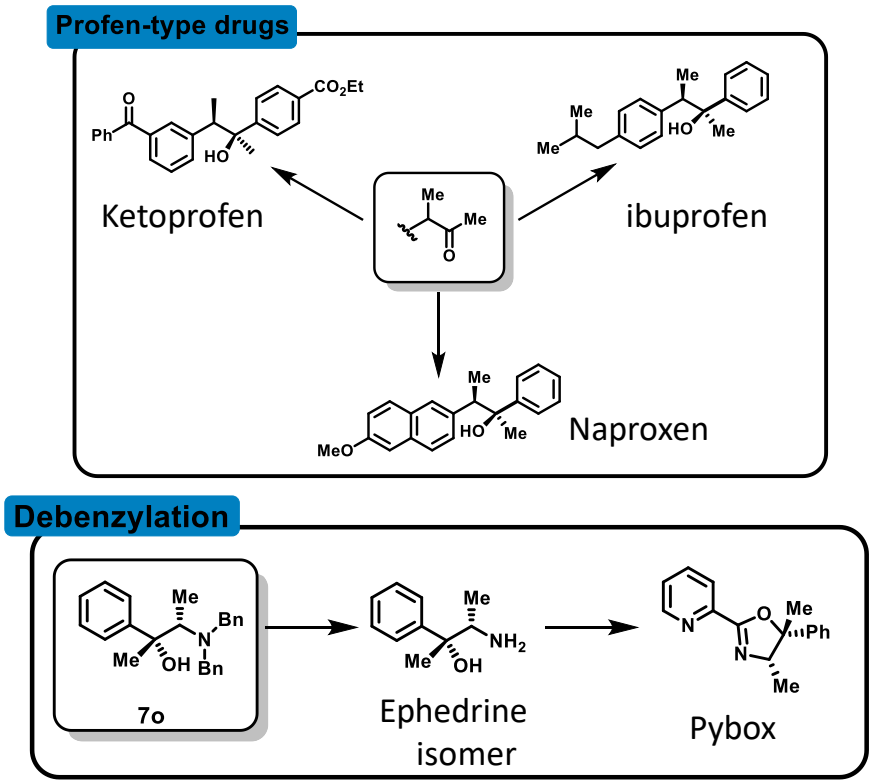
12h, 80%, 94% ee

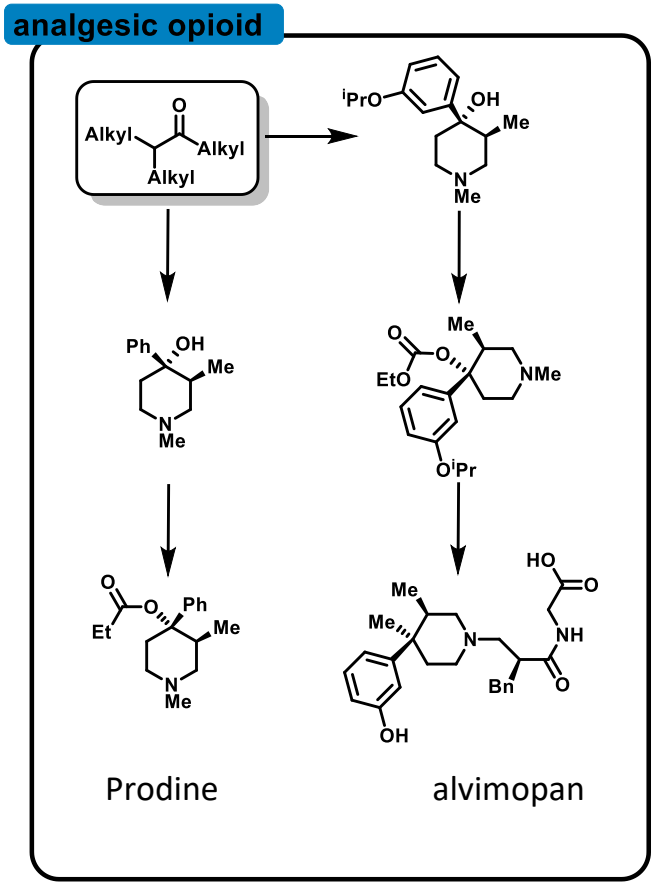
Scope

Scope conclusion:

- Substrates low racemization, **limits enantioconvergence**.
- **Bulky** or **flexible** substituents = hard for catalyst to differentiate enantiomers.
- **Bulky** or **electron-neutral** groups near reactive center can lead to low reactivity
- Functional groups that interact poorly with catalyst diminish yields

Use as a Precursor





Critical analysis: Novelty

Strong points

- **Broad substrate scope**: wide array of ketones (α-aryl, α-alkyl, α-amino, and α-oxy) and organoboronates.
- **High diastereo- and enantioselectivity** (>20:1 dr, up to 98% ee)
- First **DyKAT** on nonactivated ketones

Weak points

- **DyKAT** already established
- **Known reaction**
- **NHC ligand = known**

Critical analysis: Practicability

Strong points

- **Mild reaction conditions** (often RT to 50°C, no need for strong base or glovebox)
- **Gram-scale** and **low catalyst** loading (1–5 mol%) and air-stable precatalyst.
- Compatible on wide range of **functional** groups and **heterocycles**

Weak points

- 4 steps synthesis for the L1 ligand and under N_2 atmosphere
- Reaction times can be long (24–48 hours)

Critical analysis: Sustainability

Strong points

- Greener nucleophile (organoboronates)
- Reaction avoids **protecting** groups

Weak points

- Solvent classified as "**orange**" (cyclohexane)
- **Titanium** = metal additives are used to optimize the reaction
- Transition metal = Ni

[a] According to the Pfizer Solvent Selection Guide (Green Chem., 2008, 10, 31-36)

Questions

Question 1

What are the issues with traditional methods to achieve DyKAT on non-ativated ketones by carbon nucleophile addition? Why is it better with the approach described in this work.

Question 2

How is it possible that one enantiomer of the starting material reacts faster, but recovered starting material is always racemic? (Open question)

Question 3

Which other pathways for substrate racemization could be envisaged and which control experiments were done to exclude them?