

Asymmetric Cross-Coupling Reactions of Alkyl Electrophiles

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Introduction

- Cross-coupling: beyond the formation of Csp^2-Csp^2 bonds
- Alkyl electrophiles: A brief history
- Enantioselective cross-coupling – activated electrophiles (Negishi)
- Cross-coupling of secondary alkyl halides: Mechanistic insights
- Enantioselective cross-coupling – unactivated electrophiles (Suzuki–Miyaura)
- Secondary–secondary cross-coupling
- Conclusions and future directions

Palladium- and Nickel-Catalysed Cross-Coupling

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"for palladium-catalysed cross couplings in organic synthesis"

Powerful tools for carbon–carbon bond formation in natural product synthesis, pharmaceutical chemistry, materials science, etc.

Beyond the Formation of C_{sp}²–C_{sp}² Bonds

- Tremendous effort has gone into developing efficient sp²–sp² couplings
- Until recently, relatively few reports of cross-couplings of alkyl electrophiles

Alkyl–alkyl bonds are more common than aryl–aryl bonds

Mechanism of Palladium-Catalysed Cross-Coupling

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- “Activated” electrophiles that lack β -hydrogens are suitable substrates, e.g.

Cross-Coupling of Alkyl Electrophiles: A (very) Brief History

- 1971 – Kochi reports Cu-catalysed reaction of alkylmagnesiums with unactivated alkyl bromides (and Fe-catalysed reaction with vinyl halides)

J. K. Kochi, M. Tamura *J. Am. Chem. Soc.* **1971**, *93*, 1483 and 1485.

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- 1995 – Knochel: Ni-catalysed coupling of alkylzincs with primary iodides

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N. Miyaura, A. Suzuki *Chem. Lett.* **1992**, 691.

A. Devasagayaraj, T. Studemann, P. Knochel *Angew. Chem. Int. Ed Engl.* **1995**, 34, 2723.

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■ 2001 – Fu: Coupling of alkyl bromides/alkylboranes

- Mild reaction conditions, suppressed β -elimination.

M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu *J. Am. Chem. Soc.* **2001**, *123*, 10099.

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■ 2001 – Fu: Coupling of alkyl bromides/alkylboranes

- Mild reaction conditions, suppressed β -elimination.

■ 2002 – Kambe: Alkyl chlorides/organomagnesiums

- Later extended to alkyl fluorides (Ni/Cu)

M. R. Netherton, C. Dai, K. Neuschutz, G. C. Fu *J. Am. Chem. Soc.* **2001**, *123*, 10099.

J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe *J. Am. Chem. Soc.* **2002**, *124*, 4222.

N. Kambe *Chem. Soc. Rev.*, **2011**, *40*, 4937. (Review: alkyl electrophiles)

R. Jana, T. P. Pathak, M. S. Sigman *Chem. Rev.*, **2011**, *111*, 4937. (Review: alkyl nucleophiles)

Cross-Coupling of Alkyl Electrophiles

- Palladium catalysis is well established for **primary** electrophiles
 - Suzuki–Miyaura (**B**) and Negishi (**Zn**) - alkyl chlorides, bromides, iodides and tosylates
 - Hiyama (**Si**) and Stille (**Sn**) - alkyl bromides and iodides
 - Cu-, Co- and Fe-catalysed reactions of Grignard reagents with alkyl electrophiles

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- Secondary electrophiles: Ni-catalysed reactions

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Catalyst-controlled Enantioselective Cross-Coupling

- Early work: Csp²–Csp³ coupling of secondary nucleophiles/organomagnesiums
- 1982: Kumada
- 2001: Lemaire

T. Hayashi, M. Kumada et al. *J. Am. Chem. Soc.* **1982**, *104*, 180.

S. Pellet-Rostaing, M. Lemaire et al. *Tetrahedron: Asymmetry.* **2001**, *12*, 1983.

Nickel-Catalysed Asymmetric Negishi Reactions

- Cross-coupling of secondary alkyl *electrophiles*
- α -Bromoamides/primary organozinc halides

- Recovered starting material is racemic – stereoconvergent process

Nickel-Catalysed Asymmetric Negishi Reactions

- Secondary benzylic halides (1-bromoindanes)

- Alkyl chlorides: high ee, reduced yield.

Nickel-Catalysed Asymmetric Negishi Reactions

- Secondary allylic chlorides

- Symmetrical and (functionalised) asymmetrical substrates. Regioselectivity >20:1

Nickel-Catalysed Asymmetric Negishi Reactions

- *Arylation of secondary propargylic halides*

Nickel-Catalysed Asymmetric Negishi Reactions

- Arylation/Alkenylation of secondary α -bromonitriles

- Low temperature reactions

J. Choi, G. C. Fu *J. Am. Chem. Soc.* **2012**, *134*, 9102.

Nickel-Catalysed Asymmetric Coupling: Kumada–Corriu

- Arylation of secondary α -bromoketones with organomagnesiums

- Aryl, heteroaryl and alkyl ketones. Products can be derivatised without racemization.

Nickel-Catalysed Asymmetric Coupling

- Alkenylation of secondary α - bromoketones with organozirconium reagents

- Catalyst control

Asymmetric Negishi Cross-Coupling: Oxygen Leaving Groups

- Arylation of secondary propargylic carbonates
 - *Precedent: Organomagnesium reagents with allylic alcohol derivatives only**

Nickel-Catalysed Asymmetric Cross-Coupling

- Secondary benzylic bromides/trialkynylindium reagents

- 1-Bromoindanes also viable substrates

Asymmetric Negishi Reactions of Alkyl Electrophiles

- Application to synthesis

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T. K. Jones et al. *J. Med. Chem.* **1999**, *42*, 210

D. L. Wright, C. A. Anderson et al. *J. Med. Chem.* **2007**, *50*, 940.

Asymmetric Negishi Reactions of Alkyl Electrophiles

- *Formal synthesis of fluvirucinine A₁*

Asymmetric Negishi Reactions of Alkyl Electrophiles

- *Formal synthesis of fluvirucinine A₁*
 - 8 step enantioselective synthesis
 - Two asymmetric cross-couplings,
 - (>95% ee)
 - >20:1 regioselectivity, >98% ee, 15:1 dr

Cross-Coupling of Secondary Alkyl Electrophiles

Mechanistic considerations

- Nickel: Oxidative addition by odd-electron intermediates has been suggested

- Asymmetric catalysis

Asymmetric Negishi Reactions: Mechanistic Insights

- Vicic: Alkyl electrophiles under Negishi-like conditions

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- Evidence against a simple Ni(0)–Ni(II) mechanism

G. D. Jones, C. McFarland, T. J. Anderson, D. A. Vicic *Chem. Commun.* **2005**, 4211.

Possible Catalytic Cycle: Nickel-Catalysed Csp³–Coupling

- Ni(I)-Ni(III) mechanism:

D. A. Vacic et al. *J. Am. Chem. Soc.* **2006**, *128*, 13175.
X. Lin, D. L. Phillips *J. Org. Chem.* **2008**, *73*, 3680. (*in silico*)
Z. Li, Y -Y. Jiang, Y. Fu *Chem. Eur. J.* **2012**, *18*, 4345. (*in silico*)

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Cross-Coupling of Unactivated Secondary Alkyl Halides

- 2007: Alkyl–alkyl Suzuki–Miyaura cross-coupling of unactivated alkyl bromides

Cross-Coupling of Unactivated Secondary Alkyl Halides

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- Role of base
 - μ_2 -alkoxo-bridged transition state
- Increased reactivity (transmetallation) and **attenuation of basicity**.

Asymmetric Suzuki Cross-Coupling: Acylated Alcohols

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- Enantioselective arylation of unactivated halides

- “Reversed” sulfonamide

Asymmetric Suzuki Cross-Coupling: Sulfone-directed

- First example of sulfone-directed, metal-catalyzed enantioselective C–C bond formation

Asymmetric Alkyl–Alkyl Cross-Coupling

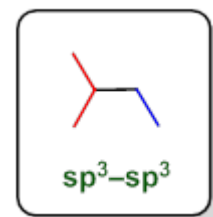
- Homologated electrophiles

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N. A. Owston, G. C. Fu. *J. Am. Chem. Soc.* **2010**, *132*, 11908.

A. Wilsily, F. Tramutola, N. A. Owston, G. C. Fu. *J. Am. Chem. Soc.* **2012**, *134*, 5794.

Asymmetric Suzuki Cross-Coupling: γ -Haloamides

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Asymmetric Suzuki Cross-Coupling: Activated Electrophiles

- Arylation of α -Bromoamides

Asymmetric Suzuki Cross-Coupling: Activated Electrophiles

■ Arylation of α -Bromoamides

- Derivatisation

- Complimentary to Negishi/Kumada –Corriu arylations

Asymmetric Suzuki Cross-Coupling: Amine (Nitrogen) Directed

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- Competition experiments indicate arylamine does not govern relative *reactivity*

Asymmetric Suzuki Cross-Couplings: Mechanistic Insights

- *Rate law*: **First order** in catalyst, organoborane. **Zeroth order** in electrophile

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- *Rate law*: **First order** in catalyst, organoborane. **Zeroth order** in electrophile
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- If complexation precedes oxidation addition, it is likely reversible.

Asymmetric Suzuki Cross-Couplings: Mechanistic Insights

- Stereoconvergence

- Suggests that halide abstraction (oxidative addition) is irreversible under these conditions

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- Stereoconvergence

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- Further evidence for a radical mechanism

- Proximal electron withdrawing group = no product.
- Unlikely to be steric as reasonably hindered substrates are viable coupling partners

Asymmetric Cross-Coupling: *Secondary-Secondary*

- Further evidence for a radical mechanism

- Consistent with a common radical intermediate in the cyclization step (all processes)

- In addition, secondary alkyl electrophiles > primary electrophiles in kinetic experiments

Asymmetric Cross-Coupling: *Secondary-Secondary*

- Benzylic bromides/alkylzinc reagents

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- Benzylic bromides/alkylzinc reagents

- Isomerization via β -hydride elimination / β -migratory insertion of Ni-alkyls

Asymmetric Cross-Coupling: *Secondary–Secondary*

- Possible Mechanism

Conclusions

- Cross-coupling of alkyl electrophiles (including those with β -hydrogens) is a reliable method for the formation of carbon-carbon bonds
- Enantioselective variants are potentially very powerful synthetic tools
- Future: Secondary nucleophilic coupling partners
- Tertiary halides = quaternary centres
- Mechanistic investigations – origin of enantioselectivity

