



中国科学院上海有机化学研究所
Shanghai Institute of Organic Chemistry, CAS

Transition-Metal-Free Coupling Reactions



Junkai Guo (郭军凯)

September 28th, 2015

The Hu Group

This report is based on a recent review:
Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**,
114, 9219–9280.

Outline

√. Introduction

— *From Transition-Metal-catalyzed coupling reactions to Transition-Metal-Free Cross-Coupling reactions*

√. Transition-Metal-Free Cross-Coupling Reactions

— *Base-Promoted HAS-Type Coupling Reactions*

— *Transition-Metal-Free Cross-Coupling of Grignard Reagents*

— *Transition-Metal-Free Oxidative Coupling Reactions*

√. Summary and Outlook

Introduction



理查德·赫克

(Richard F. Heck)



根岸 英一

(Ei-ichi Negishi)



鈴木 章

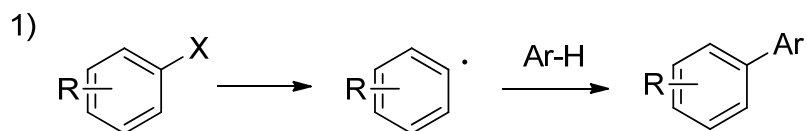
(Akira Suzuki)

Achievement: *one of the most efficient and direct strategies for C-C bond formation*

Drawbacks: *a. Cat and ligands are expensive, sometimes difficult to prepare;
b. toxic to different extents and removal is quite costly and challenging;
c. sensitive to oxygen and moisture, thus manipulation is strict;
d. do not meet the requirement of sustainable development.*

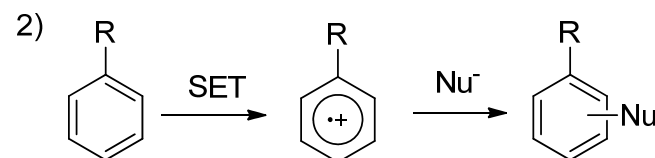
Transition-metal-free coupling reactions: used to describe coupling reactions, which employ similar starting materials and give similar results with those catalyzed by transition-metal catalysts, while during the process no transition-metal catalysts were used.

Scheme 1: Typical Transition-Metal-Free Coupling Reactions through Various Pathways



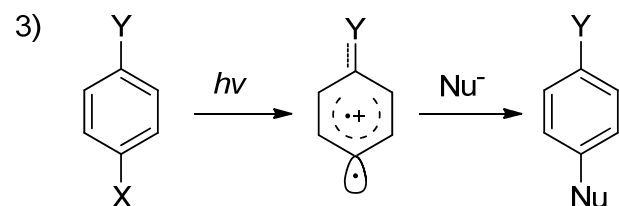
X=I,Br,Cl,N₂⁺,OOR,etc.

radical pathway



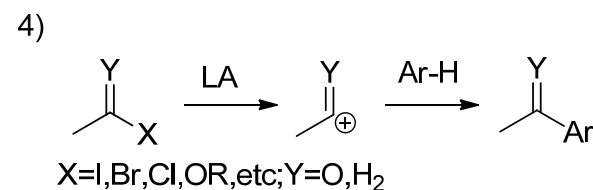
R=electron-donating group

radical cation pathway



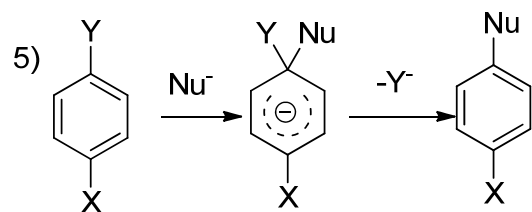
X=I,Br,Cl,F,N₂⁺,OR,etc.; Y=electron-donating group

cationic pathway



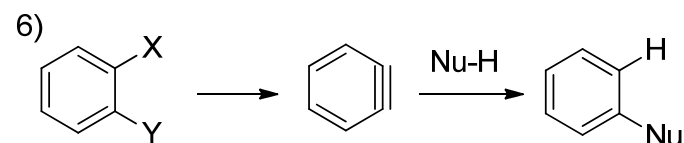
X=I,Br,Cl,OR,etc.; Y=O,H₂

electrophilic aromatic substitution



Y=I,Br,Cl,F,OR,etc.; X=electron-donating group

nucleophilic aromatic substitution



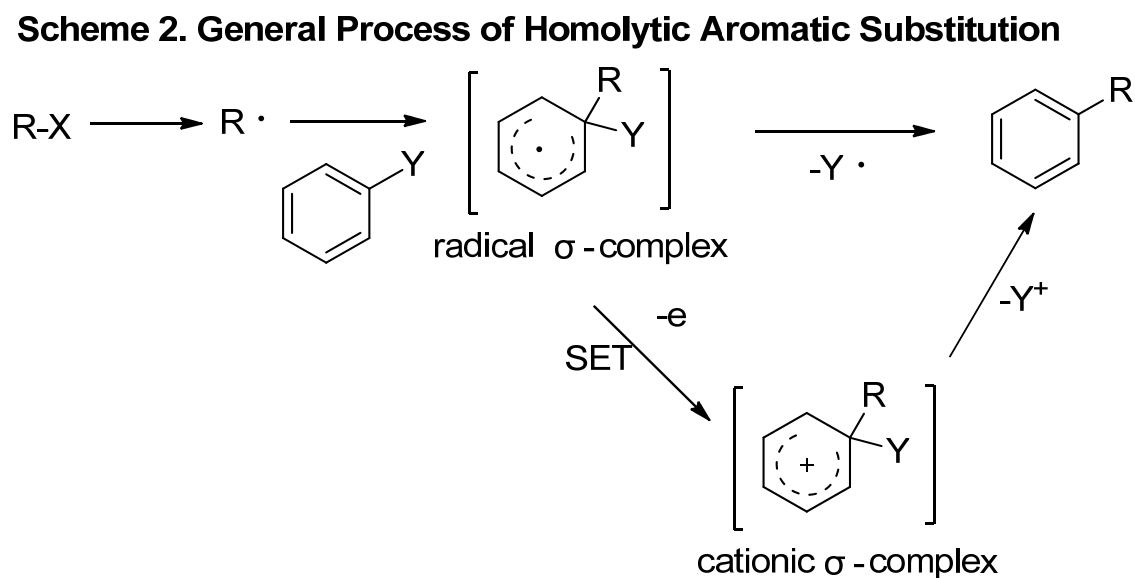
aryne pathway

7)
Organocatalysis

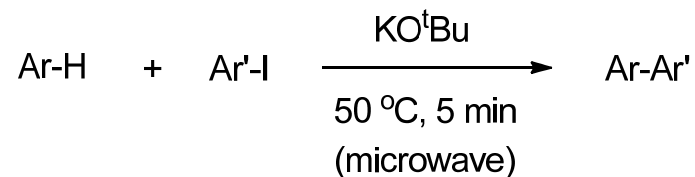
Transition-Metal-Free Cross-Coupling Reactions: Base-Promoted HAS-Type Coupling Reactions

Homolytic aromatic substitution reactions (HAS) : defined as the replacement of a leaving group Y on an aromatic ring by an attacking radical species.

Williams, G. H. *Homolytic Aromatic Substitution*; Pergamon: Oxford, 1960.



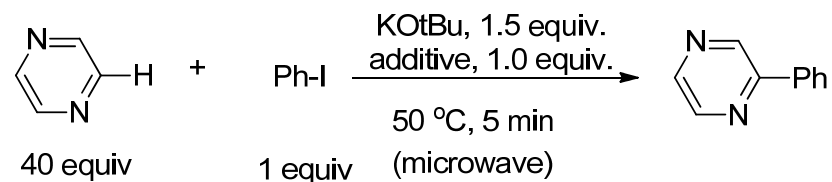
Base-Promoted HAS-Type Coupling Reactions



Itami, K. *et al. Org. Lett.* 2008, 10, 4673.

Ar=N-containing heteroarenes; Ar'=arenes

KOtBu-Promoted Coupling Reactions with Radical Scavengers

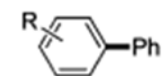
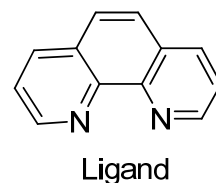
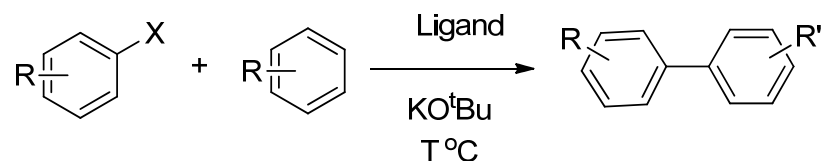


additive	yield
none	98%
galvinoxyl	<1%
TEMPO	<1%
acrylonitrile	<1%

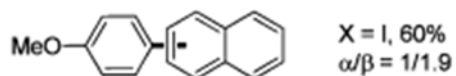
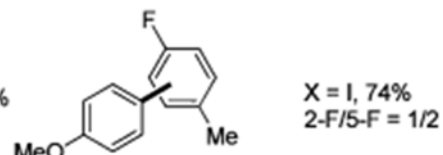
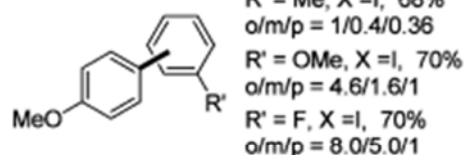
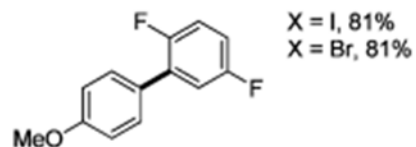
a mechanism of an HAS reaction was plausible. This report is the first beautiful example of base promoted transition-metal-free cross-coupling between aryl halides and N-containing heteroarenes.

Bsae-Promoted HAS-Type Coupling Reactions

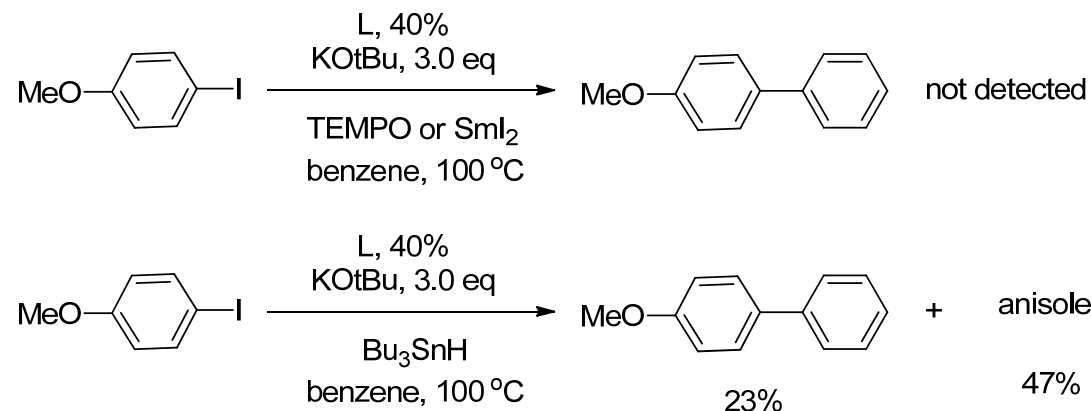
Table 1. Cross-Couplings of Aryl Iodides/Bromides with Common Arenes^a



R = 4-MeO, X = I, 83%
 R = 4-MeO, X = Br, 86%
 R = 3-MeO, X = I, 81%
 R = 2-MeO, X = I, 73%
 R = H, X = Br, 74%
 R = 4-Me, X = I, 69%
 R = 4-Me, X = Br, 89%
 R = 3-Me, X = Br, 82%
 R = 2-Me, X = I, 52%
 R = 2-Me, X = Br, 44%
 R = 3,5-Me, X = I, 74%
 R = 3,5-Me, X = Br, 59%
 R = 3,5-Me-4-MeO, X = Br, 77%
 R = 4-Ph, X = I, 89%
 R = 4-OCF₃, X = I, 89%
 R = 4-F, X = I, 78%
 R = 4-Cl, X = I, 82%
 R = 3-CF₃, X = I, 42%
 R = 4-CN, X = I, 36%
 R = 4-CN, X = Br, 72%
 R = 4-Bz, X = Br, 68%



Scheme 3. Experiments Involving Radical Scavengers or Reductants



^aThe reactions of bromides were carried out on the scale of 0.5 mmol of aryl bromides in the presence of 40 mol % **9a** and 3.0 equiv of KO^tBu in 4 mL of arenes (if liquid) at 100 °C for 18–24 h. The reactions of iodides were carried out on the scale of 0.2 mmol of aryl iodides in the presence of 20 mol % **9a** and 2.0 equiv of KO^tBu in 2 mL of benzenes at 100 °C for 24 h. The reactions of various arenes were carried out on the scale of 0.5 mmol of aryl halides in the presence of 40 mol % **9a** and 3.0 equiv of KO^tBu in 80 equiv of arenes at 120 °C for 48 h.

Mechanism of Base-Promoted HAS Reaction

Scheme 4 . Mechanism of Base-Promoted HAS Reaction

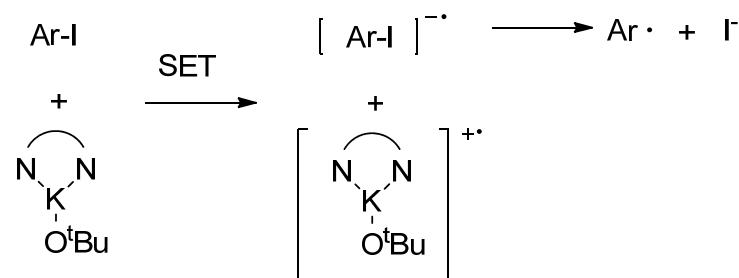
several important key steps:

(a) the generation of an aryl radical;

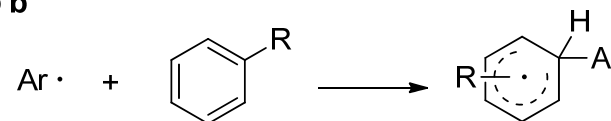
(b) the addition of aryl radical to an arene;

(c) the transfer of electron and proton to afford coupling products.

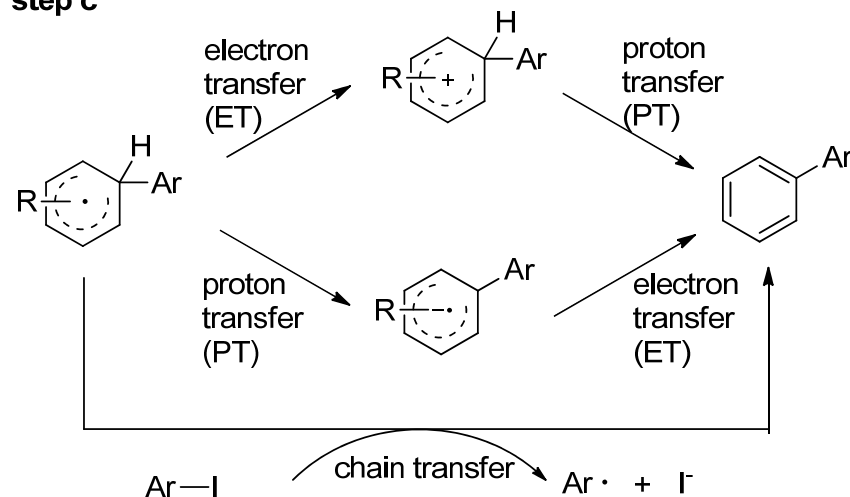
step a



step b

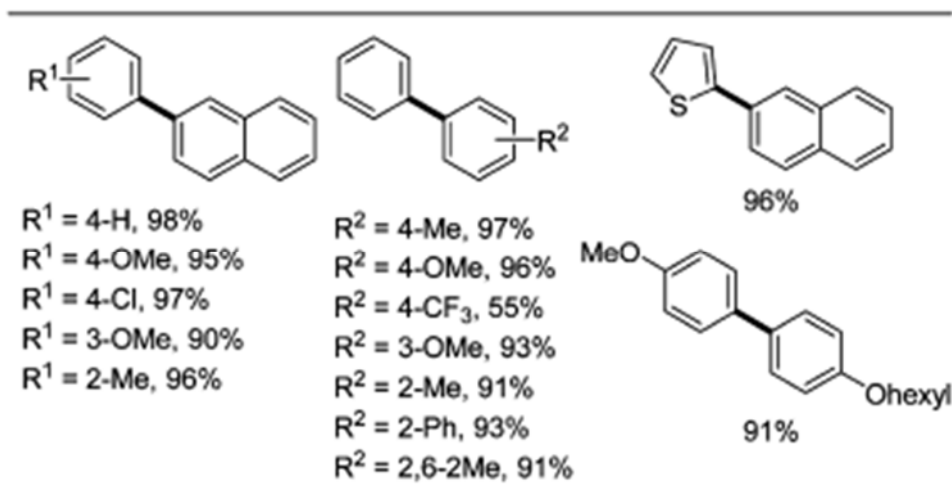
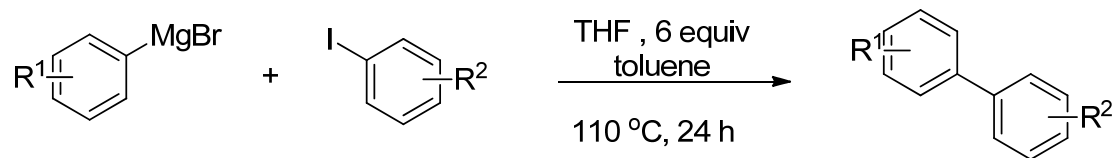


step c



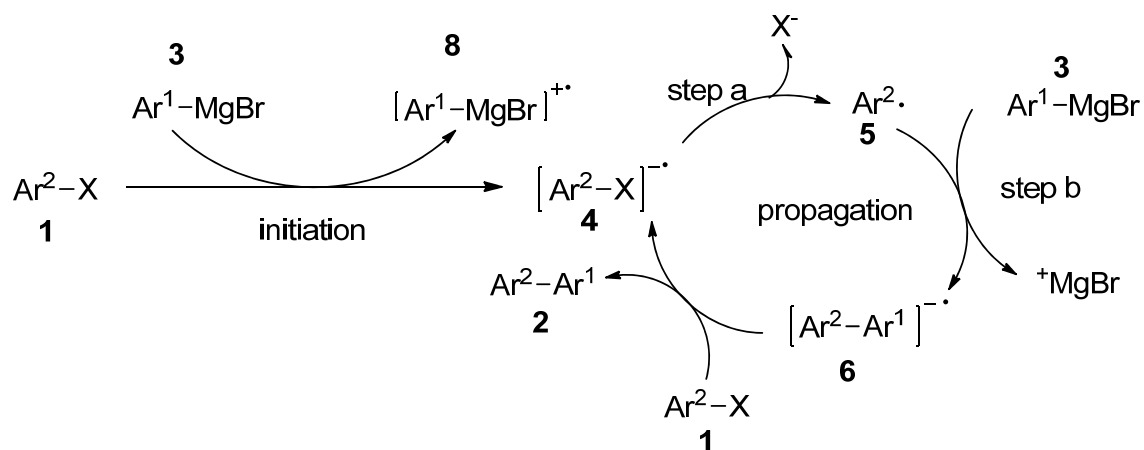
Transition-Metal-Free Cross-Coupling of Grignard Reagents

Table 2. Cross-Coupling Reactions of Various Aryl Grignard Reagents with Aryl Halides.

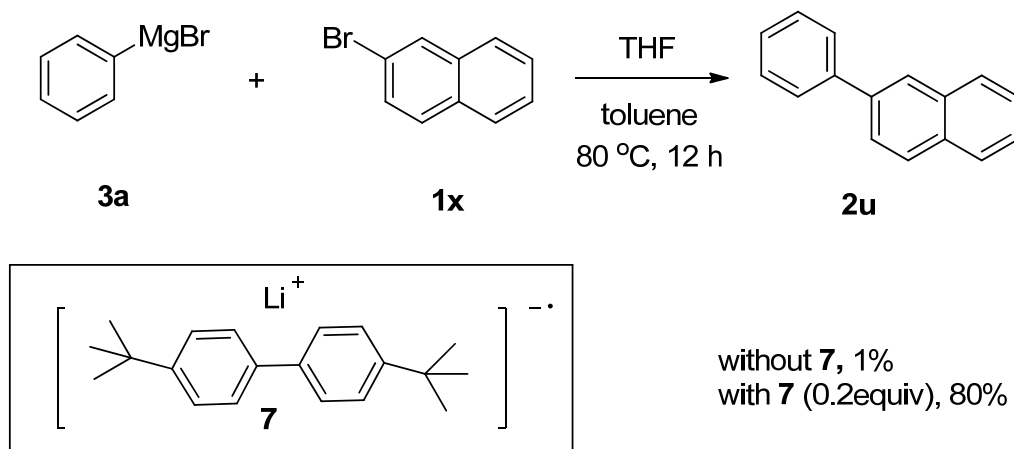


Cross-Coupling of Aryl Grignard Reagents with Aryl Halides through $S_{RN}1$ Pathway

Scheme 5. $S_{RN}1$ Pathway of the Coupling of Aryl Grignard Reagents with Aryl Halides



Scheme 6. Reaction of PhMgBr and 2-Bromoanaphthalene at 80°C



This result indicated that the biaryl anion intermediate **6** played a role in a single electron donor in the propagation step, which was faster than the initiation step.

Electrophilic Amination between Aryl Grignard Reagents and N-Chloroamines

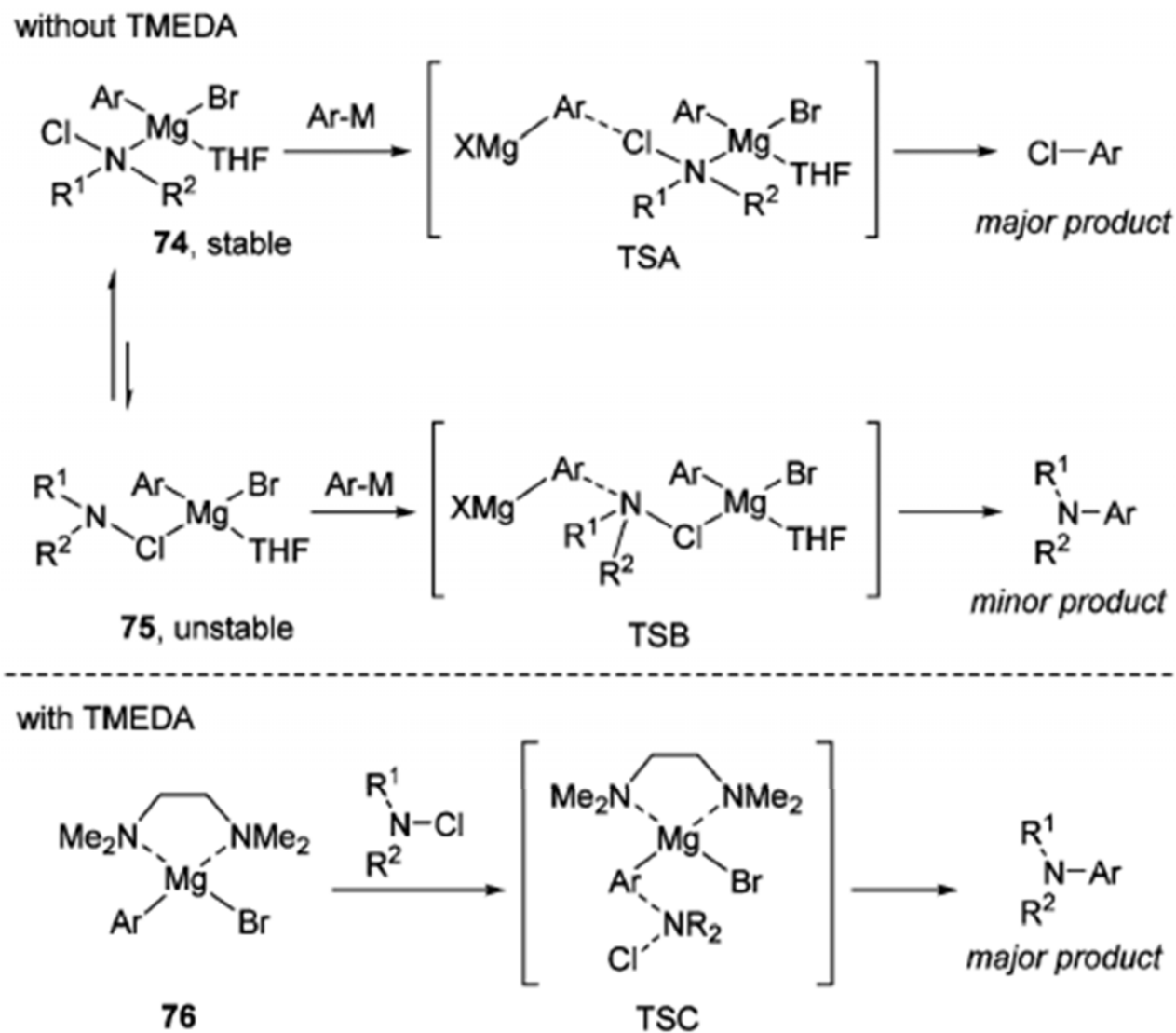
Table 3. Electrophilic Amination between Aryl Grignard Reagents and N,N-Dialkyl-N-chloroamines

entry	N-Chloroamine	ArMgX	equiv of TMEDA	yield
1			3.0	88%
2			3.0	84%
3			10	78%
4			1.5	89%
5			6.0	88%
6			6.0	49%

the additive **TMEDA** played a key role in controlling the chemoselectivity as show in next PPT.

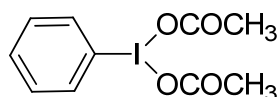
Electrophilic Amination between Aryl Grignard Reagents and N-Chloroamines

Scheme 7. Possible Mechanism of the Electrophilic Amination between Aryl Grignard Reagents and N-Chloroamine

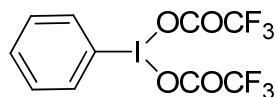


Transition-Metal-Free Oxidative Coupling Reactions: Hypervalent-Iodine-Mediated Oxidative Coupling Reactions

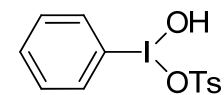
Hypervalent Iodine Reagents



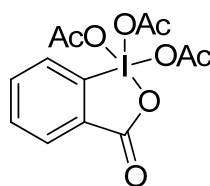
PIDA



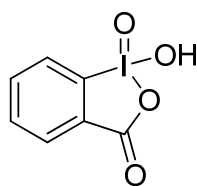
PIFA



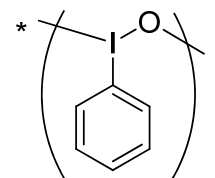
HTIB
Koser's reagent



DMP



IBX

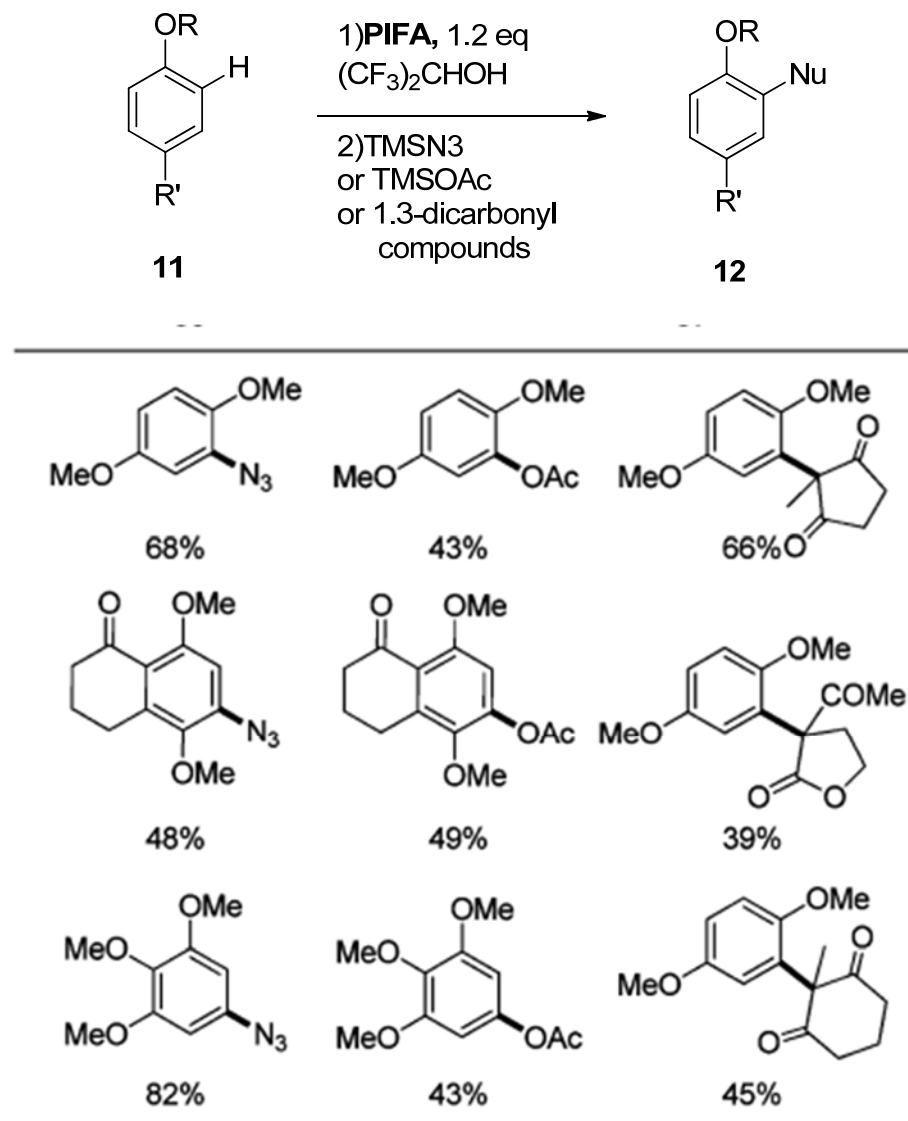


iodosobenzene

due to their low toxicity, high stability, easily handling, and now commercial availability, they served as a useful synthetic oxidant in organic synthesis and became highly welcome both in chemical industry and laboratories.

Hypervalent-Iodine-Mediated Oxidative Homocoupling for Carbon–Carbon Bond Formation.

Table 4. C-H Functionalizations with Azides, Acetates, and 1,3-Dicarbonyl Compounds



first reported a hypervalent iodine-induced nucleophilic substitution of para-substituted phenol ethers

Kita, Y. *et al.* *J. Am. Chem. Soc.* 1994, 116, 3684.

Hypervalent-Iodine-Mediated Oxidative Homocoupling for Carbon–Carbon Bond Formation.

Scheme 8. General Process of the Hypervalent Iodine(III) Reagents Promoted Oxidative Coupling Reactions



these polar and low-nucleophilic protic solvents could efficiently stabilize the reactive cationic intermediates and prevent the possible competitive side-reactions

confirmed by UV and ESR spectroscopic studies

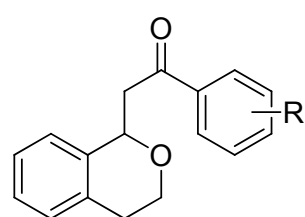
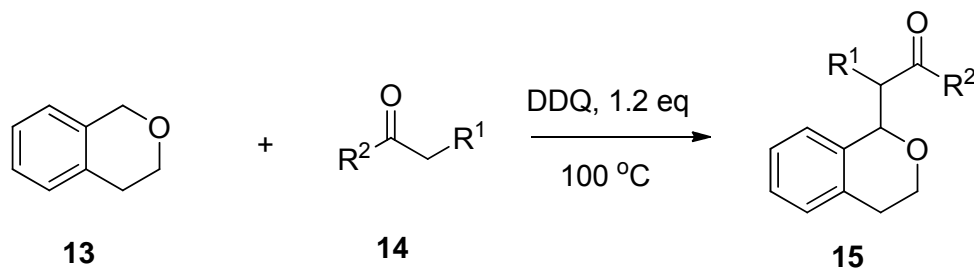
Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* 1996, 68,627.

Fritz, H. P.; Gebauer, H. Z. *Naturforsch., B: J. Chem. Sci.* 1978,338, 702.

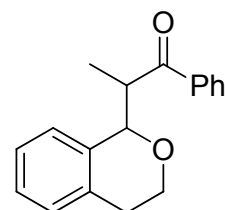
DDQ-Promoted Oxidative Coupling Reactions

first example of DDQ-mediated direct cross-dehydrogenative-coupling (CDC) reaction between benzyl ethers and simple ketones

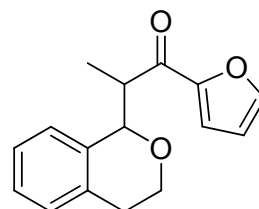
Table 5. DDQ-Mediated Direct Cross-Dehydrogenative-Coupling (CDC) Reaction between Isochroman and Simple Ketones



R=H, 69%
R=4-Me, 65%
R=4-Br, 68%
R=4-OMe, 53%
R=2-Br, 60%
R=2-OH, 30%



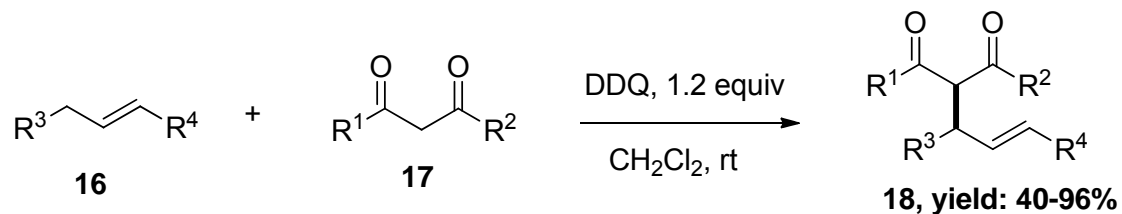
75%



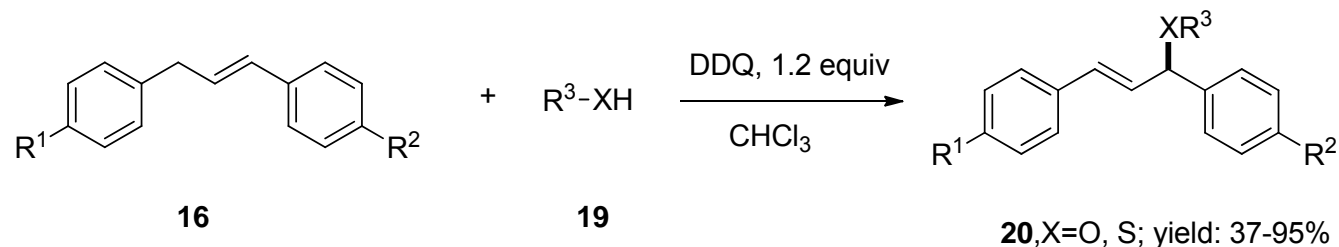
69%

DDQ-Promoted Oxidative Coupling Reactions

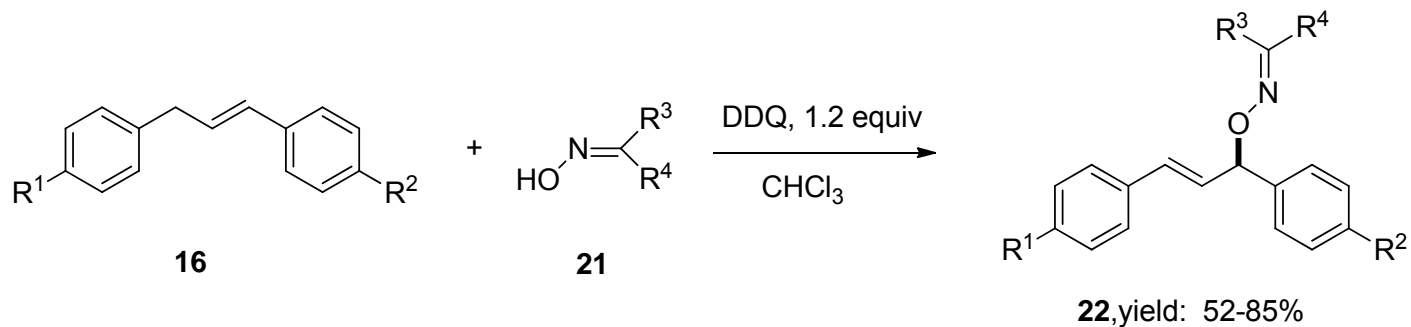
Scheme 9. DDQ-Promoted Oxidative Coupling Reactions between Allylic sp³ C-H and Various Nucleophiles



(a) Bao, W. L. *et al. Adv. Synth. Catal.* 2008, 350, 1263. (b) Bao, W. L. *et al. J. Org. Chem.* 2008, 73, 6881.



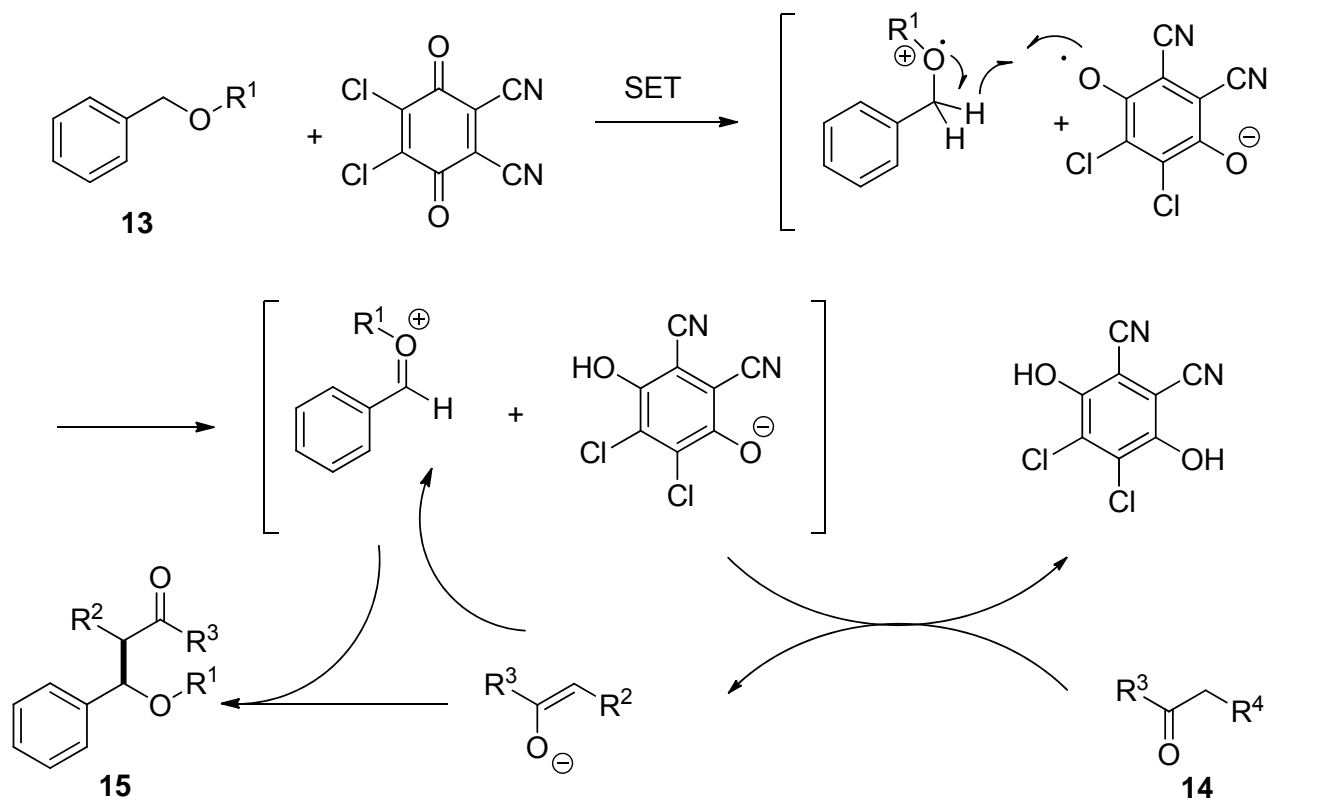
(a) Bao, W. L. *et al. Adv. Synth. Catal.* 2009, 351, 865. (b) Bao, W. *et al. Tetrahedron* .2011, 67, 4793.



Bao, W.-L. *et al. Eur. J. Org. Chem.* 2010, 1235.

DDQ-Promoted Oxidative Coupling Reactions

Scheme 10. Tentative Mechanism for DDQ-Mediated Direct Cross-Dehydrogenative-Coupling (CDC) Reaction



Summary and Outlook

1. Recent advances on the transition-metal-free coupling reactions have been introduced and discussed .

2. transition-metal-free coupling reactions display higher efficiency under simpler and milder conditions than those in transition-metal-catalyzed editions. However, the chemoselectivity and regioselectivity are usually not satisfactory due to the intrinsic mechanistic limitation. And it doesn't have a more flexible modification and colorful synthetic stories.

Because of the endless pursuit of sustainable chemistry and green chemistry, anyway, the step chasing new conditions and new systems of highly efficient and selective transition-metal-free reactions should be never ceased.

Thank you for your attention