

Construction of C-C or C-N Bond via C-H Activation ~Chemistry of Yong-Qiang Tu~

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1. Yong-Qiang Tu's Profile

Education & Work experience:

- | | |
|-----------|---|
| 1958 | Born in Guizhou Province, China |
| 1978-1982 | B.S. Organic Chemistry
Lanzhou University, China |
| 1982-1985 | M.S. Organic Chemistry
Lanzhou University, China |
| 1985-1989 | Ph.D. Organic Chemistry
Lanzhou University, China |
| 1993-1995 | Post-Doctoral Fellow
Queensland University, Australia; Advisor: Prof. W. Kitching
Visiting Professor
Bielefeld University, Germany |
| 1995- | Professor of Chemistry
Lanzhou University, China |
| 2001- | Director of State Key Lab of Applied Organic Chemistry
Lanzhou University, China |



Research Interest:

1. Synthetic studies of the biologically active marine natural products
2. Tandem reaction and its application to total synthesis of bioactive alkaloids
3. Studies on the construction of C-C or C-N bond via the C-H activation (since 2005)

Awards & Honors:

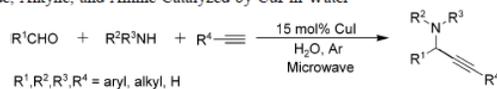
1. 1992 Chinese Chemical Society Prize for Young Chemist
2. 1993 2nd Prize of Progress in Science and Technology, by the Education Council of China
3. 2000 Outstanding Youth Scholarship Award, by Qiu Shi Science & Technology Foundation, Hong Kong, P. R. China
4. 2002 1st Prize of Progress in Science and Technology, by the Gansu Province
5. 2005 Lilly Scientific Excellence Award in China, by Eli Lilly & Company
6. 2006 1st Natural Science Prize, by Gansu Province
7. 2009 Member of the Chinese Academy of Sciences

2-1. C-H Activation by Cu

Microwave-Promoted Three-Component Coupling of Aldehyde, Alkyne, and Amine
via C-H Activation Catalyzed by Copper in WaterLei Shi, Yong-Qiang Tu*, Min Wang, Fu-Min Zhang, and Chun-An Fan,
Org. Lett., **2004**, *6*, 1001.

Advantages:

- (i) Microwave (MW)-promoted, in water---Green chemistry!
- (ii) It required only the cheaper CuI as catalyst without Au, Ag, or other additives.
- (iii) It was applicable to a broader substrate scope
(both aromatic and aliphatic aldehydes and secondary amines).
- (iv) It proceeded faster and gave good to high yield, and its experimental process was simple and easy.

Table 1. Coupling of Aldehyde, Alkyne, and Amine Catalyzed by CuI in Water^a

entry	R ¹	amine (R ² , R ³)	R ⁴	product	time (min)	yield (%) ^b
1	Ph	morpholine	Ph	1a	20	90
2	2-FC ₆ H ₄	morpholine	Ph	1b	20	89
3	2-ClC ₆ H ₄	morpholine	Ph	1c	20	88
4	3-ClC ₆ H ₄	morpholine	Ph	1d	20	90
5	4-ClC ₆ H ₄	morpholine	Ph	1e	20	91
6	4-BrC ₆ H ₄	morpholine	Ph	1f	20	90
7	4-MeC ₆ H ₄	morpholine	Ph	1g	30	82
8	4-MeOC ₆ H ₄	morpholine	Ph	1h	30	85
9	4-NO ₂ C ₆ H ₄	morpholine	Ph	1i	5	41
10	2-furyl	morpholine	Ph	1j	20	86
11	1-naphthyl	morpholine	Ph	1k	20	88
12	cyclohexyl	morpholine	Ph	1l	20	90
13	<i>n</i> -C ₃ H ₇	morpholine	Ph	1m	20	78
14	Ph	pyrrolidine	Ph	2a	10	93
15	Ph	piperidine	Ph	2b	20	91
16	Ph	R ² = R ³ = Et	Ph	2c	20	90
17	Ph	R ² = R ³ = (Me) ₂ CH	Ph	2d	20	83
18	Ph	R ² = R ³ = <i>c</i> -C ₆ H ₁₁	Ph	2e	20	75
19	Ph	R ² = R ³ = Ph	Ph	2f	10 ^c	0 ^c
20	Ph	R ² = Bn, R ³ = Me	Ph	2g	20	83
21	Ph	R ² = Ph, R ³ = H	Ph	2h	10	85
22	Ph	R ² = (Me) ₂ C, R ³ = H	Ph	2i	10	76
23	Ph	morpholine	<i>n</i> -C ₅ H ₁₁	3a	20	83
24	Ph	morpholine	TMS	3b	20	80 ^d
25	Ph	morpholine	CH ₂ OTBS	3c	20	86

^a For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. ^b Isolated yields based on the aldehyde. ^c No desired product was obtained. ^d Under solvent-free conditions.

Details of the process:

- In 2003, the team developed a MW-promoted coupling reaction of aromatic halides and amines. (Tu *et al. Org. Lett.* **2003**, *5*, 3515.)
- Although several methods for construction of such units in water were reported, some required expensive Au or Ag as catalyst, while some were limited to only one kind of aldehyde or the aromatic aldehyde and primary amine.
- For the aldehyde substrate scope, morpholine and phenylacetylene were used as model substrates (entries 1-13).
- For the amine substrate scope, benzaldehyde and phenylacetylene were used as model substrates (entries 14-22).
- For the alkyne substrate scope, benzaldehyde and morpholine were used as model substrates (entries 23-25).
- They found MW irradiation was necessary, because without MW, the coupling under heating required more than 5 days.

Preparation of CuI



Procedure

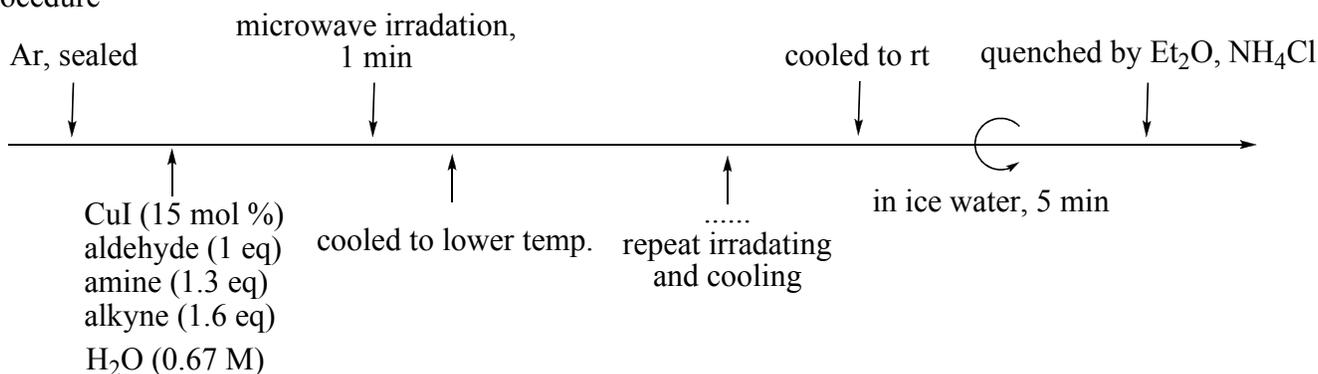
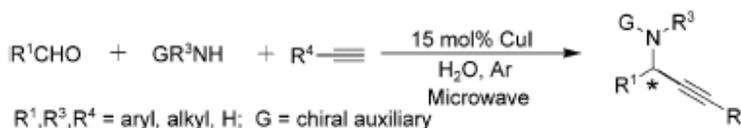
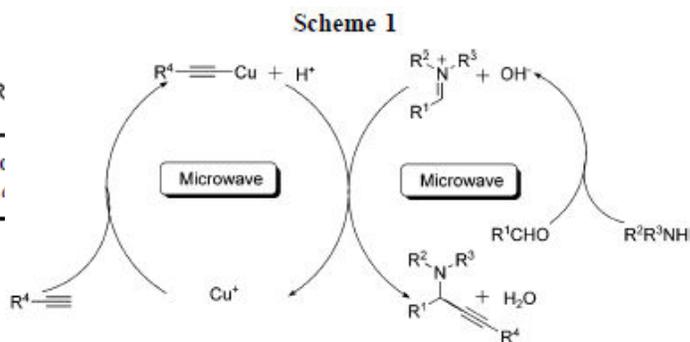


Table 2. Diastereoselective A³ Coupling Induced with Chiral Amine Substrate^a



entry	R ¹	amine (G, R ³)	R ⁴ product	dr ^b	yield (%) ^c
1	Ph	(S)-proline methyl ester	Ph 4a	95:5	88
2	Ph	G = (S)-Ph(CH ₃)CH, R ³ = H	Ph 4b	67:33	83
3	Ph	G = (S)-Ph(CH ₃)CH, R ³ = Bn	Ph 4c	67:33	81

^a For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. ^b Diastereomeric ratio (dr) was determined by ¹H NMR; the absolute configuration has been not determined. ^c Isolated yields based on the aldehyde.



2-2. C-H Activation by Rh (Pd)

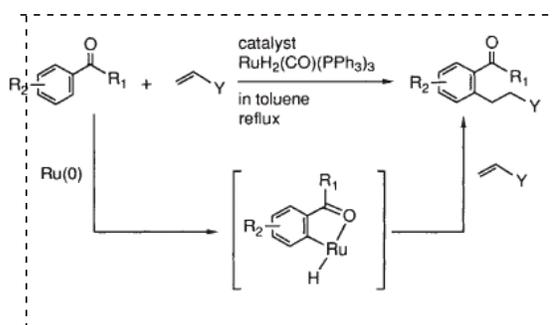
2-2-1. A Reaction for sp³-sp³ C-C Bond Formation via Cooperation of Lewis Acid-Promoted/Rh-Catalyzed C-H Bond Activation

Lei Shi, Yong-Qiang Tu*, Min Wang, Fu-Min Zhang, Chun-An Fan, Yu-Ming Zhao, and Wu-Jiong Xia
J. Am. Chem. Soc. **2005**, *127*, 10836-10837.

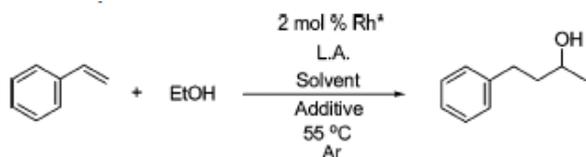
They were inspired by the landmark report of the ruthenium catalyzed hydroarylation of alkenes by Murai and co-workers
Murai S. *et al.* *Nature* **1993** *366* 529-531

TABLE 1. Addition of aromatic ketones to olefins catalyzed by RuH₂(CO)(P(C₆H₅)₃)₃

Run	Aromatic ketone	Olefin	Ketone/olefin/catalyst (mmol)	Time (h)	Product	Yield (%)	Product	Yield (%)
1			2 / 2 / 0.04	0.2		75		8
2			2 / 6 / 0.04	90		<1		94
3			2 / 4 / 0.04	4		(66)		
4		CH ₂ =CH ₂ (6 kg cm ⁻²)	2 / 12 / 0.04	2		100		
5			2 / 10 / 0.12	4		100		
6			2 / 10 / 0.12	33		96		



Scheme 1. Optimization Studies



Entry	Rh*	L.A.	Solvent	Additive	Olefin:EtOH	Yield (%) ^b
1 ^a	RhCl(PPh ₃) ₃	---	Toluene		1:10	0
2 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	Toluene		1:10	27
3 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	Benzene		1:10	24
4 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	Toluene		1:1	21
5 ^c	RhCl ₃	BF ₃ ·OEt ₂	Toluene		1:10	20
6 ^d	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	Toluene	PPh ₃	1:10	0
9 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	DME		1:10	0
10 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	DMF		1:10	0
11 ^c	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	DMSO		1:10	0
12 ^c	RhCl(PPh ₃) ₃	TiCl ₄	Toluene		1:10	0
13 ^c	RhCl(PPh ₃) ₃	Ti(Oi-Pr) ₃	Toluene		1:10	0
14 ^c	RhCl(PPh ₃) ₃	CuCl ₂	Toluene		1:10	0
15 ^c	RhCl(PPh ₃) ₃	BF ₃ ·N ^t Bu ₃	Toluene		1:10	0
16 ^{c,e}	RhCl(PPh ₃) ₃	BEt ₃	Toluene	Air	1:10	0
17 ^c	RhCl(PPh ₃) ₃	B(Oi-Pr) ₃	Toluene		1:10	0
18 ^c	---	BF ₃ ·OEt ₂	Toluene		1:10	0
19 ^f	RhCl(PPh ₃) ₃	BF ₃ ·OEt ₂	Toluene	BuBr	1:10	70

Procedure

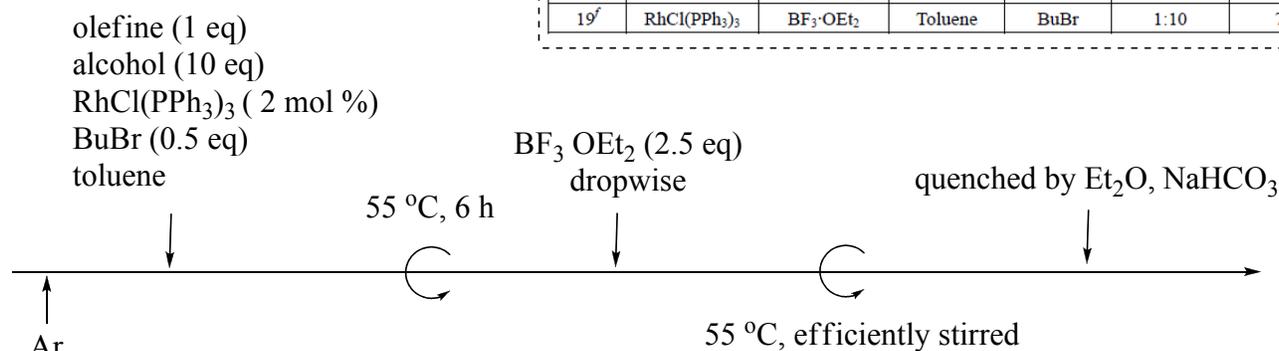
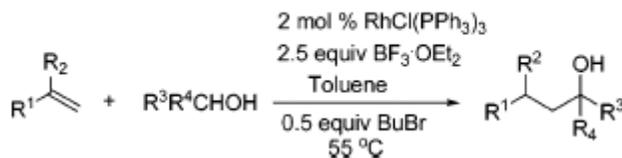


Table 1. Coupling of Alcohols with Olefins^a



entry	olefin (R ¹ , R ²)	alcohol (R ³ , R ⁴)	product	yield (%) ^b	entry	olefin (R ¹ , R ²)	alcohol (R ³ , R ⁴)	product	yield (%) ^b
1	R ¹ = Ph, R ² = H	R ³ = CH ₃ , R ⁴ = H	1a	70	10	R ¹ = 4-OMeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1i	c
2	R ¹ = Ph, R ² = H	R ³ = <i>n</i> -Pr, R ⁴ = H	1b	70	11	R ¹ = 4-(CH ₂ Cl)C ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1j	71
3	R ¹ = Ph, R ² = H	R ³ = <i>i</i> -Pr, R ⁴ = H	1c	68	12	R ¹ = 1-naphthyl, R ² = H	R ³ = CH ₃ , R ⁴ = H	1k	73
4	R ¹ = Ph, R ² = H	R ³ = <i>n</i> -C ₁₃ H ₂₇ , R ⁴ = H	1d	74	13	R ¹ = 2-ClC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1l	66
5	R ¹ = 2-MeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1e	65	14	R ¹ = 2-BrC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1m	64
6	R ¹ = 3-MeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1f	78	15	R ¹ = 2-NO ₂ C ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1n	31 ^e
7	R ¹ = 4-MeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1g	63	16	R ¹ = Ph, R ² = Ph	R ³ = CH ₃ , R ⁴ = H	1o	64
8	R ¹ = 2-OMeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	c		17	R ¹ = CH ₃ , R ² = CH ₃	R ³ = <i>n</i> -C ₇ H ₁₅ , R ⁴ = H	1p	31 ^e
9	R ¹ = 3-OMeC ₆ H ₄ , R ² = H	R ³ = CH ₃ , R ⁴ = H	1h	57	18	R ¹ = Ph, R ² = H	R ³ = CH ₃ , R ⁴ = CH ₃	1q	c

Mechanism supporting experiments:

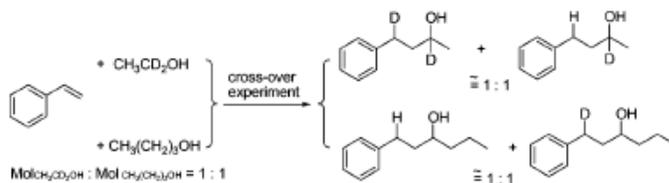
RhCl₃/BF₃OEt₂/toluene could make the reaction occur.
 ---> The formation of Rh(III) intermediates.

Addition of PPh₃ (0.05 equiv) could prevent the reaction.
 --->The presence of PPh₃ could prohibit the ligand dissociation and exchange.

The crossover experiment was performed using styrene and a 1:1 mixture of deuterated and undeuterated alcohols (Scheme 2).

--->A possible radical reaction mechanism was involved, which would lead to a statistical distribution of the labels in the products.

Scheme 2. Deuterium Crossover Experiment



The addition of radical scavenger (1,4-benzoquinone, TEMPO, and

FeCl₃) in the system of ethanol with styrene prohibited the reaction.

--->The presence of a radical reaction mechanism was further confirmed.

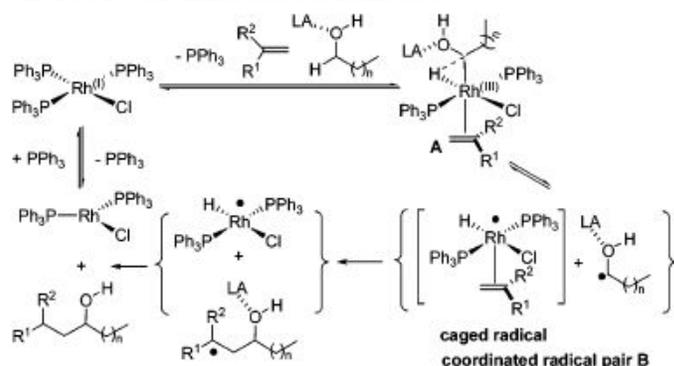
4-phenylbutan-2-one could not have been observed in the cross-coupling of ethanol and styrene (entry 1, Table 1).

--->The reaction could not undergo the reaction mechanism as reported in the hydroacylation of olefins with alcohols: first hydrogen transfer from alcohol to form aldehyde.

When acetaldehyde was used in place of the primary alcohol, the reaction could not proceed under the same condition.

--->The first hydrogen transfer from alcohol to form aldehyde was not the proper mechanism.

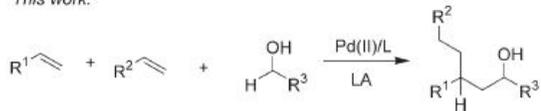
Scheme 3. Plausible Reaction Mechanism



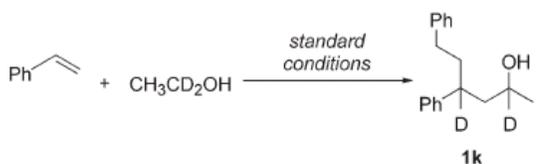
2-2-2. Palladium-Catalyzed/Lewis Acid-Promoted Alkene Dimerization and Cross-Coupling with Alcohols via C-H Bond Activation

Yi-Jun Jiang, Yong-Qiang Tu*, En Zhang, Shu-Yu Zhang, Ke Cao, and Lei Shi, *Adv. Synth. Catal.* **2008**, 350, 552.

This work:



Scheme 1. Cross-coupling of alcohols to alkenes via C-H activation.



Scheme 2. Deuterium labeling experiment.

Table 1. Optimization of reaction condition.^[a]

Entry	Catalyst	Solvent	Product (yield [%]) ^[b]	2a
1	Pd(OAc) ₂	Toluene	0	10
2	Pd(OAc) ₂ /PPh ₃ (1:2)	Toluene	8	0
3	Pd(OAc) ₂ /PPh ₃ (1:2)	CH ₂ Cl ₂	10	0
4	Pd(OAc) ₂ /PPh ₃ (1:2)	CH ₃ NO ₂	35	0
5	Pd(OAc) ₂ /PPh ₃ (1:1.5)	CH ₃ NO ₂	50	0
6 ^[c]	Pd(OTFA) ₂ /PPh ₃ (1:1.5)	CH ₃ NO ₂	60	0
7 ^[d]	Pd(acac) ₂ /PPh ₃ (1:1.5)	CH ₃ NO ₂	30	0
8 ^[e]	Pd(dba) ₂ /PPh ₃ (1:1.5)	CH ₃ NO ₂	0	16
9 ^[f]	Pd(OTFA) ₂ /P(Mesityl) ₃ (1:1.5)	CH ₃ NO ₂	20	0
10 ^[g]	Pd(OTFA) ₂ /dppp (1:1.5)	CH ₃ NO ₂	5	5

^[a] Reaction conditions: styrene (3.0 mmol), ethanol (15.0 mmol), catalyst (0.3 mmol), acid (7.5 mmol) and solvent (12 mL) at 60 °C for 20 h.

Table 2. Domino synthesis of γ -branched secondary alcohols.^[a]

Entry	Substrate	Product	Yield [%] ^[b]	Entry	Substrate	Product	Yield [%] ^[b]
1	R ¹ , R ² =Ph, R ³ =Me	1a	60 ^[c] (1:0.6)	7	R ¹ , R ² = <i>m</i> -C ₆ H ₄ Me, R ³ =Me	1g	51 (1:0.8)
2	R ¹ , R ² =Ph, R ³ = <i>i</i> -Pr	1b	40 (1:0.8)	8	R ¹ , R ² = <i>p</i> -C ₆ H ₄ Me, R ³ =Me	1h	56 (1:0.6)
3	R ¹ , R ² =Ph, R ³ = <i>n</i> -Bu	1c	53 (1:0.7)	9	R ¹ , R ² = <i>m</i> -C ₆ H ₄ Cl, R ³ =Me	1i	30 ^[d] (1:0.6)
4	R ¹ , R ² =Ph, R ³ = <i>n</i> -C ₁₃ H ₂₇	1d	45 (1:0.5)	10	R ¹ =Ph, R ² = <i>n</i> -C ₆ H ₁₃ , R ³ =Me	1j	27 ^[e] (1:0.8)
5	R ¹ , R ² =Ph, R ³ = <i>c</i> -Hexyl	1e	68 ^[d] (1:0.7)				
6	R ¹ , R ² =Ph, R ³ =CH ₂ CH ₂ Ph	1f	70 (1:0.8)				

^[a] Standard reaction conditions: 3 (1.5 mmol), 3' (1.5 mmol), 4 (15.0 mmol), Pd(OTFA)₂ (0.3 mmol), PPh₃ (0.45 mmol), BF₃·OEt₂ (7.5 mmol) and CH₃NO₂ (12 mL) at 60 °C for 20 h.

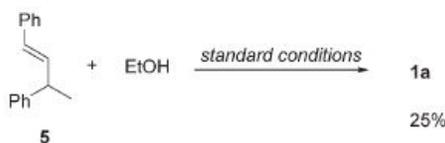
^[b] Isolated yields calculated on the basis of olefine 3; the ratio of two diastereoisomers determined by ¹HNMR is given in parenthesis.

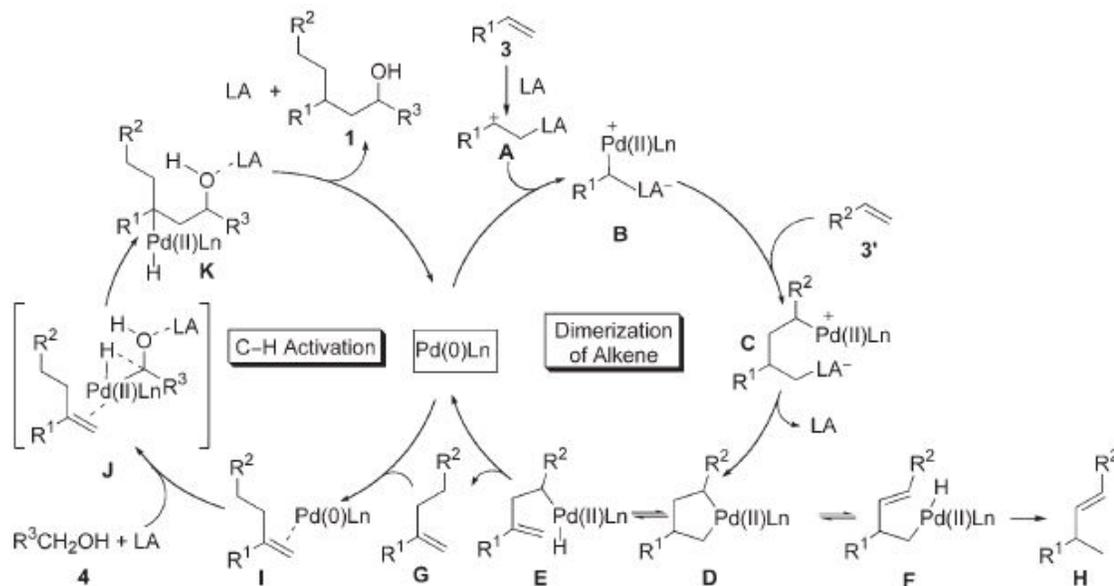
^[c] The ratio of two diastereoisomers is calculated by isolated yields.

^[d] Reaction time: 8 h.

^[e] Reaction time: 48 h.

A supporting experiment using the isolated alkene 5





Scheme 3. Plausible mechanism for C-H activation and the domino reactions.

2-2-3. Cross-Coupling Reaction between Alcohols through sp^3 C-H Activation Catalyzed by a Ruthenium/Lewis Acid System

Shu-Yu Zhang, Yong-Qiang Tu*, Chun-An Fan, Yi-Jun Jiang, Lei Shi, Ke Cao, and En Zhang, *Chem. Eur. J.* **2008**, *14*, 10201.

Equation 1.

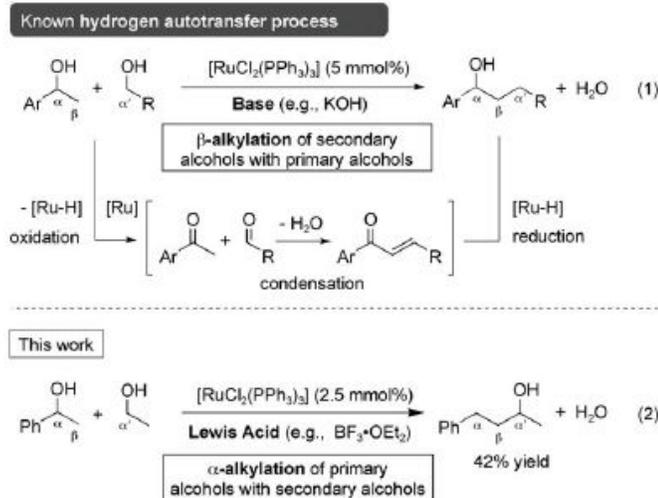


Table 1. Optimization of reaction conditions.^[a]

Entry	Catalyst	Acid	Solvent	Yield[%] ^[b]
1	IrCl ₃	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	trace
2	RuCl ₃	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	trace
3	[RhCl(PPh ₃) ₃]	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	72
4	[Pd(OAc) ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	22
5	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	82
6	[RuCl ₂ (PPh ₃) ₂]	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	64
7	[AuCl(PPh ₃) ₃]	BF ₃ ·OEt ₂	Cl(CH ₂) ₂ Cl	trace
8	[RuCl ₂ (PPh ₃) ₃]	InCl ₃	Cl(CH ₂) ₂ Cl	15
9	[RuCl ₂ (PPh ₃) ₃]	TsOH	Cl(CH ₂) ₂ Cl	[-]
10	[RuCl ₂ (PPh ₃) ₃]	SnCl ₄	Cl(CH ₂) ₂ Cl	62
11	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	toluene	68
12	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	THF	[-]
13	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	CH ₃ NO ₂	60
14	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂	CH ₃ CN	[-]
15	[RuCl ₂ (PPh ₃) ₃]	BF ₃ ·OEt ₂ ^[d]	Cl(CH ₂) ₂ Cl	42

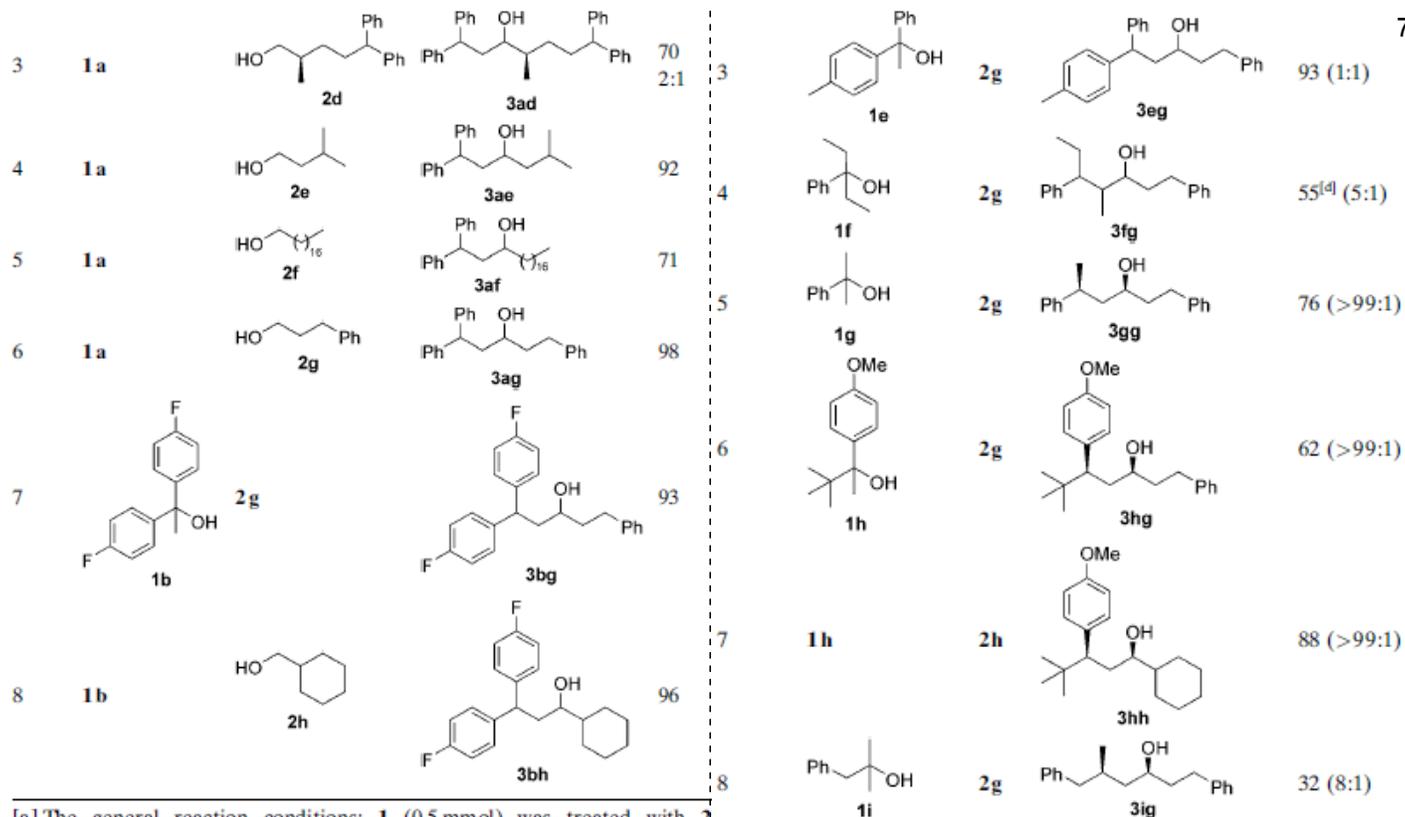
[a] For entries 1–14, the general reaction condition: 1,1-diphenylethanol **1a** (0.5 mmol) reacted with ethanol **2a** (0.75 mmol) in the presence of catalyst (0.0125 mmol) and acid (0.6 mmol) at 50 °C for 5 h. [b] Yield of isolated product. [c] No desired product. [d] BF₃·OEt₂ (0.3 equiv), 4 days.

Table 2. α -Alkylation of various primary alcohols with tertiary alcohols.^[a]

Entry	Substrates	Product	Yield [%] ^[b]
1	1a , 2b	3ab	93
2	1a , 2c	3ac	91

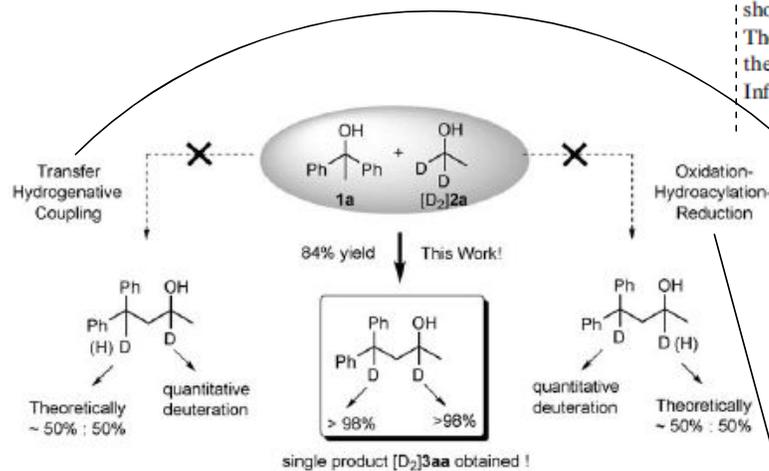
Table 3. α -Alkylation of primary alcohols with various tertiary alcohols.^[a]

Entry	Substrates	Product ^[b]	Yield [%] ^[c]
1	1c , 2g	3cg	92 (7:1)
2	1d , 2g	3dg	92 (3:2)

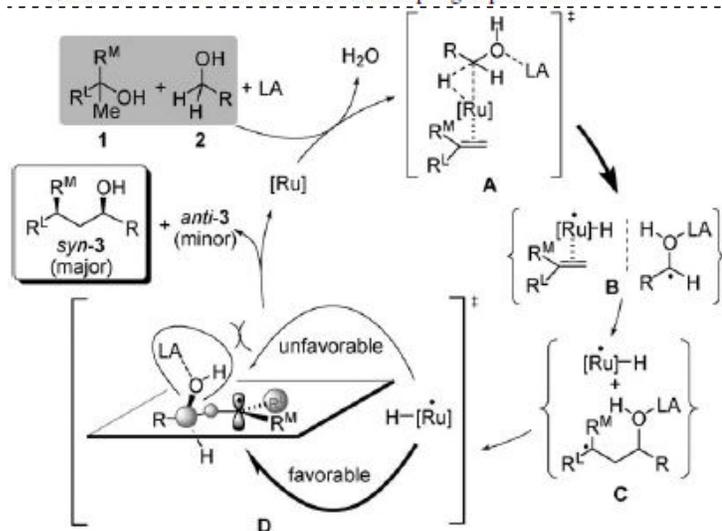


[a] The general reaction conditions: **1** (0.5 mmol) was treated with **2** (0.75 mmol) in the presence of $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.0125 mmol), and Lewis acid (0.6 mmol) at 50 °C. [b] Yield of isolated product based on the tertiary alcohol **1** used.

[a] Reaction conditions: **1** (0.5 mmol) was treated with **2** (0.75 mmol) in the presence of $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.0125 mmol), and Lewis acid (0.6 mmol) at 50 °C. [b] Major *syn* diastereoisomers with relative configuration were shown. [c] Yield of isolated product based on the tertiary alcohol **1** used. The *syn:anti* ratio of the two diastereomers is given in parentheses, and the assignment of relative configuration (see Scheme 1 in the Supporting Information). [d] Only two diastereomers were isolated, and the stereochemistry remains unknown currently.

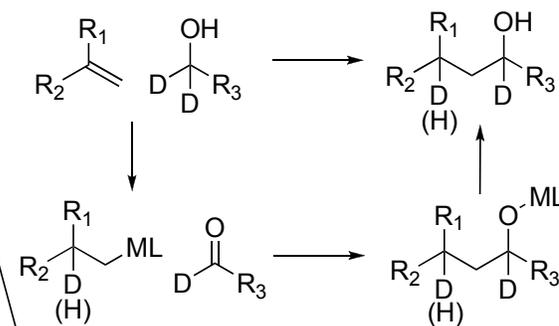


Scheme 2. Deuterium-labeled cross-coupling experiment.

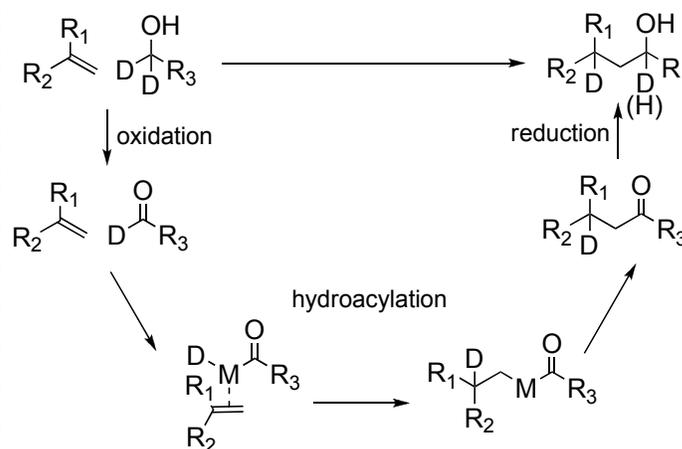


Scheme 3. Proposed catalytic mechanism.

Transfer Hydrogenative Coupling



Oxidation-Hydroacylation-Reduction



2-2-4. A Direct C-C Cross-Coupling of Alcohols at the β -Position with Aldehydes under Co-Promotion of Tris(triphenylphosphine)-rhodium Chloride/Boron Trifluoride Etherate

Shu-Yu Zhang, Yong-Qiang Tu*, Chun-An Fan, Yi-Jun Jiang, Lei Shi, and Ke Cao, *Adv. Synth. Catal.* **2008**, *350*, 2189.

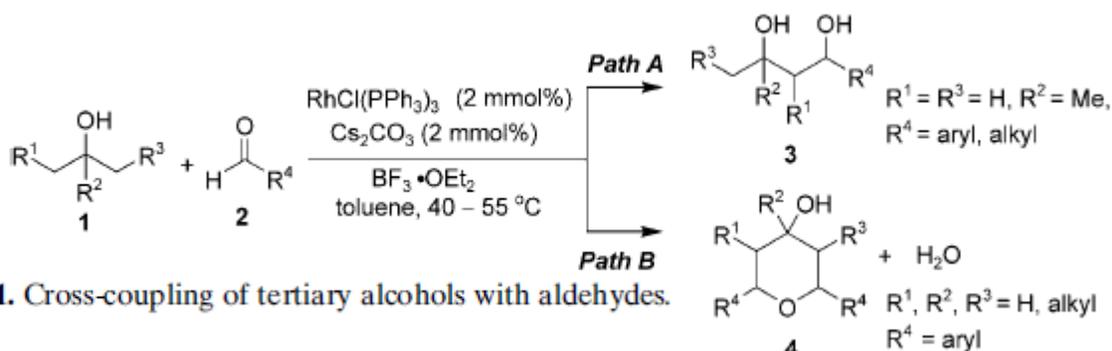


Table 1. The coupling reaction via *Path A* for synthesizing the 1,3-diol.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			65
2			76
3			47
4			74
5			55 (91 ^[c])
6			42
7			63

^[a] General conditions: **2** (1.0 mmol), **1** (2.5 mmol.), $\text{RhCl}(\text{PPh}_3)_3$ (2 mmol%), Cs_2CO_3 (2 mmol%), and $\text{BF}_3 \cdot \text{OEt}_2$ (1.5 mmol) in toluene for 3–12 h.

^[b] Isolated yield based on the aldehyde **2** used.

^[c] Yield based on recovered starting material.

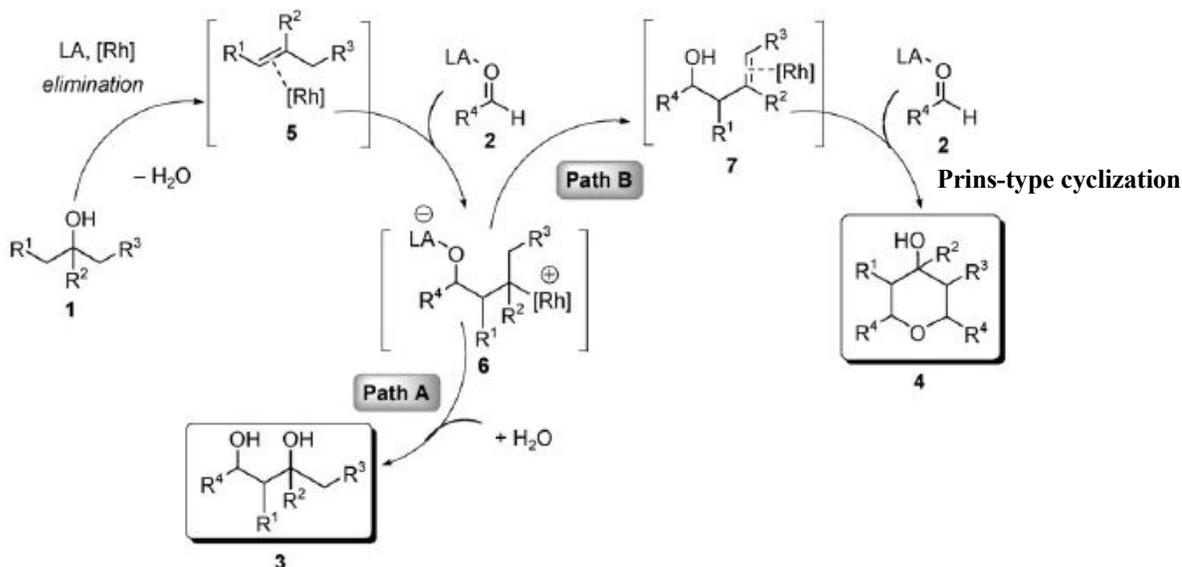
Table 2. The coupling reaction via *Path B* for synthesizing the polysubstituted THP.^[a]

Entry	Substrates	Product ^[b]	Yield
1	1a +		72
2	1a +		54
3	1b +		65
4	1c + 2a		63
5	1d + 2a		37

^[a] General conditions: **2** (1.0 mmol), **1** (2.5 mmol.), $\text{RhCl}(\text{PPh}_3)_3$ (2 mmol%), Cs_2CO_3 (2 mmol%), and $\text{BF}_3 \cdot \text{OEt}_2$ (1.5 mmol) in toluene for 3–12 h.

^[b] The *dr* of **4a** is 3:2, and for **4b–4e** only one diastereomeric form was isolated.

^[c] Isolated yield based on the aldehyde **2** used.

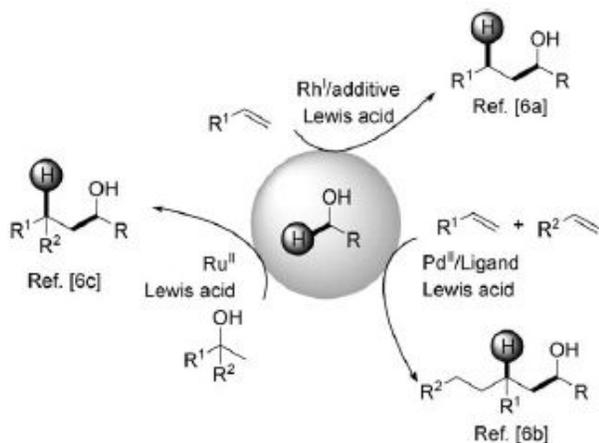


Scheme 3. Proposed pathways for the cross-coupling of tertiary alcohols with aldehydes.

2-3. C-H Activation by Fe

Iron-Catalyzed C(sp³)-C(sp³) Bond Formation through C(sp³)-H Functionalization: A Cross-Coupling Reaction of Alcohols with Alkenes

Shu-Yu Zhang, Yong-Qiang Tu*, Chun-An Fan, Fu-Min Zhang, and Lei Shi
Angew. Chem. Int. Ed. **2009**, *48*, 8761.



Scheme 1. Carbon-carbon cross-coupling reactions of alcohols with olefins through copromotion with late transition metals and Lewis acids.

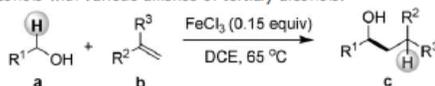
Table 1: Optimization of cross-coupling reaction conditions.^[a]

Entry	[Fe]	Solvent	3 a [%] ^[b]
1	FeCl ₃	toluene	trace
2	FeCl ₃	THF	–
3	FeCl ₃	DMF	–
4	FeCl ₃	<i>n</i> BuBr	trace
5	FeCl ₃	DCE	83
6	FeCl ₃	<i>n</i> BuBr/DCE ^[c]	63
7	FeCl ₂	DCE	22
8	Fe(acac) ₃	DCE	–
9	FeCl ₃ ·6H ₂ O	DCE	72
10	Fe(ClO ₄) ₃ ·9H ₂ O	DCE	36
11	FeCl ₃ (0.02 equiv)	DCE	42
12	FeCl ₃ (0.10 equiv)	DCE	64

-Several ligands such as TMEDA, NEt₃ and DACH, as well as some additives such as LiCl, KCl, CuI, CuCl₂, CuBr₂, Cu(OAc)₂, CuO, Cu₂O, NiCl₂·6H₂O, and CoCl₂·6H₂O were tested, but no significant improvement of the yield was observed.
-The above non-iron additives alone, in the absence of FeCl₃, did not promote this cross-coupling reaction.

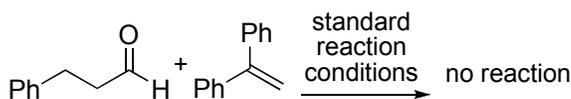
[a] General reaction conditions: a mixture of alcohol **1a** (0.2 mmol), alkene **1b** (0.3 mmol), and solvent (2 mL) in the presence of iron catalyst (0.03 mmol) was stirred at 65 °C under argon for 8–12 hours. [b] Yield of isolated product. [c] 1.0 equivalent of DCE was added to 2 mL of *n*BuBr. acac = acetylacetonate, DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran.

Table 2: Cross-coupling reaction of primary alcohols with various alkenes or tertiary alcohols.^[a]

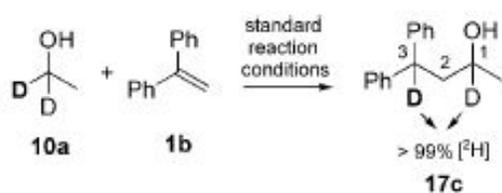


Entry	Substrate alcohol	alkene	Product	Yield [%] ^[b]	Entry	Substrate alcohol	alkene	Product	Yield [%] ^[b]
1	1a	2b	2c	83	9	9a	1b	10c	53
2	2a	1b	3c	81	10	1a	3b	11c	82
3	3a	1b	4c	72	11	1a	4b	12c	88
4	4a	1b	5c	78	12	1a	5b	13c	62 (>99:1) ^[d]
5	5a	1b	6c	70	13	1a	6b	1c	82
6	6a	1b	7c	77	14	5a	7b	14c	78
7	7a	1b	8c	51 (90) ^[c]	15	1a	8b	15c	58 (1:1)
8	8a	1b	9c	48 (92) ^[c]	16	5a	9b	16c	93 (1:1)

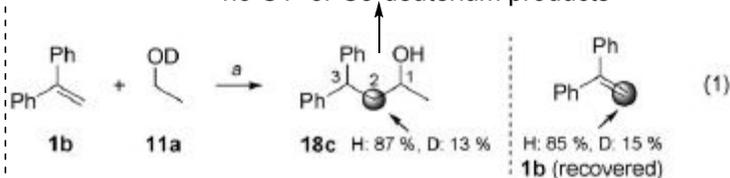
[a] Reaction conditions: alcohols **a** (0.2 mmol) were treated with alkenes **b** (0.3 mmol) in the presence of FeCl₃ (0.03 mmol) and DCE (2 mL) at 65 °C for 8–24 hours. [b] Yield of isolated product. [c] Yield based on the recovered starting material. [d] Only one diastereomer was isolated, and its relative stereochemistry is temporarily assigned as *syn* according to our previous report.^[6d]



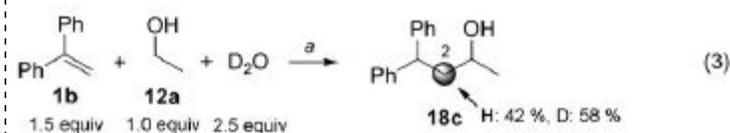
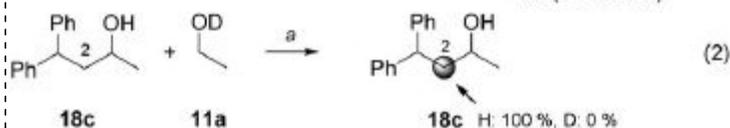
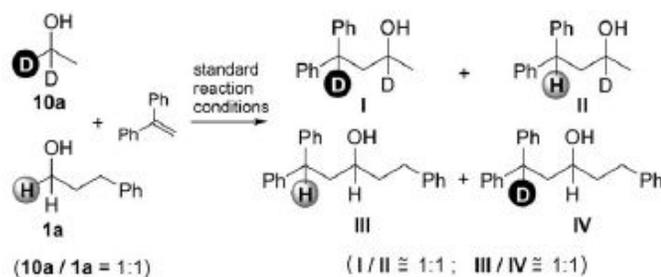
Scheme 2'



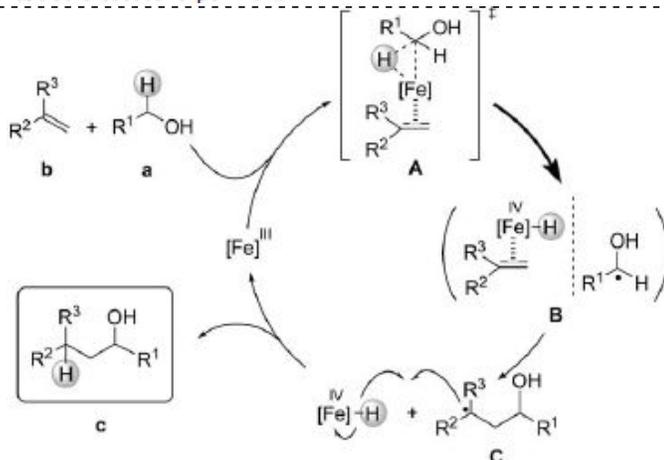
no C1- or C3-deuterium products



Scheme 2. Deuterium-labeled experiment using 10a.

Scheme 4. Deuterium-labeled experiment probing the active hydrogen atom.^[12] Reaction conditions: a) 1. standard reaction conditions, 2. aqueous work-up.

Scheme 3. Deuterium-labeled crossover experiment.



Scheme 5. Proposed catalytic mechanism.