Cross-Dehydrogenative Coupling (CDC): Exploring C-C Bond Formations beyond Functional Group Transformations

Lit. seminar 2010/07/24
M2 JianYi Wang

Prof. Chao-Jun Li

Professional Experience

2003-	**Professor of Chemistry** Canada Research Chair (Tier I) in Organic/Green Chemistry Department of Chemistry, McGill University, Montreal, Canada
2002 (Fall)	**Visiting Professor** Department of Chemistry, University of California, Berkeley, USA
2000-2003	**Professor of Chemistry** Department of Chemistry, Tulane University, New Orleans, USA
1998-2000	**Associate Professor** (with Tenure) Department of Chemistry, Tulane University, New Orleans, USA
1994-1998	**Assistant Professor** Department of Chemistry, Tulane University, New Orleans, USA
1992-1994	**NSERC Post-Doctoral Fellow** Stanford University; Advisor: Prof. B. M. Trost
1989-1992	**Ph.D. Organic Chemistry** McGill University; Advisors: Prof. Tak-Hang Chan and Prof. David N. Harpp
1985-1988	**M.S. Organic Chemistry** Chinese Academy of Science; Advisor : Prof. Tak-Hang Chan (McGill University)
1979-1983	**B.S. Chemistry** Zhengzhou University, China

Contents:

Introduction and Background

Research in three progressive stages

(1) developing Grignard-type reactions in aqueous media to simplify protection-deprotection steps. Chao-Jun Li, ***J. AM. CHEM. SOC.* 2005,** *105*, 3095

(2) developing nucleophilic addition reactions by using C-H bonds as surrogates for organometallic reagents to simplify halogenation-dehalogenation steps and avoid the utilization of a stoichiometric amount of metal for such reactions (possible in water) Chao-Jun Li, ***J. AM. CHEM. SOC.* 2007,** *106*, 2546

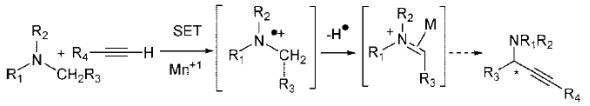
(3) developing direct C-H and C-H coupling to explore the possibility of chemical transformations beyond functionalization and defunctionalization in syntheses.

CDC Reaction Involving ¦Á-C-H Bonds of Nitrogen in Amines

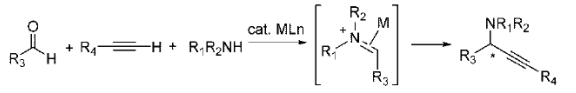
Alkynylation (sp^3-sp Coupling)

SCHEME 2

Proposed Alkynylation of α-C-H Bond of Nitrogen in Amines



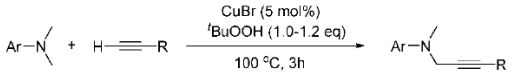
Aldehdye-Alkyne-Amine (A^3) Coupling



Starting Point:

(1) propargylic amines are of great pharmaceutical interest and are synthetic intermediates for various nitrogen compounds;
(2) the sp^3 C-H bond ¦Á to nitrogen in amines can be readily activated to generate iminium ions via single-electron-transfer (SET) processes or by transition metals as described by Leonard and Murahashi;
(3) we and others have described the aldehyde-alkyne-amine coupling (A^3) reactions to afford propargyl amines catalyzed by various transition metals via the formation of the same intermediate (Scheme 2).

SCHEME 3. Copper-Catalyzed Alkynylation of *N,N*-Dimethylanilines



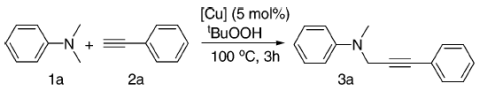
isolated yields: 12-82%

Ar= Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4

R= Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4, 4-PhC_6H_4, 2-Py, $HOCH_2$, $EtCO_2CH_2$, CH_3OCO, Bu, Ph, Ph, Ph

Chao-Jun Li, ***J. AM. CHEM. SOC.*** **2004,** *126*, 11810-11811

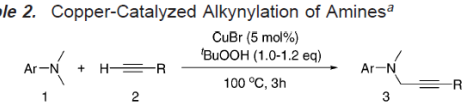
Table 1. Selection of Copper Catalyst[a]



entry	catalyst	NMR yield[b]
1	CuBr	77
2	$CuBr_2$	72
3	CuCl	75
4	$CuCl_2$	73
5	CuI	56
6	$Cu(I)_2Se$	61
7	CuOTf	25
8	$Cu(OTf)_2$	8
9	no	0

[a] 4.0 mmol aniline, 2.0 mmol phenylacetylene, 0.1 mmol copper salt, and 0.8 mL tBuOOH (5−6 M in decane). [b] Reported yields were based on alkynes and determined by NMR using an internal standard.

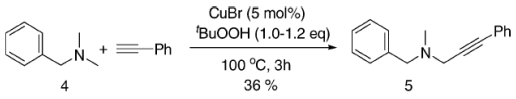
Table 2. Copper-Catalyzed Alkynylation of Amines[a]



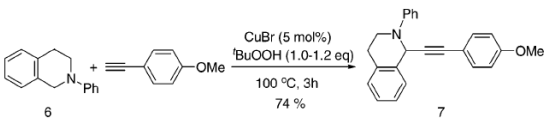
entry	Ar	R	product	yield[b]
1	Ph	Ph	3a	74
2	Ph	4-MeOPh	3b	82
3	Ph	4-MePh	3c	74
4	Ph	4-BrPh	3d	74
5	Ph	4-PhPh	3e	60
6	Ph	2-Py	3f	36
7	Ph	$HOCH_2$	3g	40
8	Ph	$EtCOOCH_2$	3h	58
9	Ph	CH_3OCO	3i	25
10	Ph	Bu	3j	12
11	4-MePh	Ph	3k	73
12	2-MePh	Ph	3l	53
13	4-BrPh	Ph	3m	69

[a] 4.0 mmol amine, 2.0 mmol alkyne, 0.1 mmol copper bromide, and 0.4 mL tBuOOH (5−6 M in decane). [b] Isolated yields were based on alkynes.

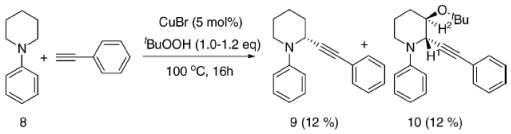
Scheme 2. Reaction of *N,N*-Dimethylbenzylamine



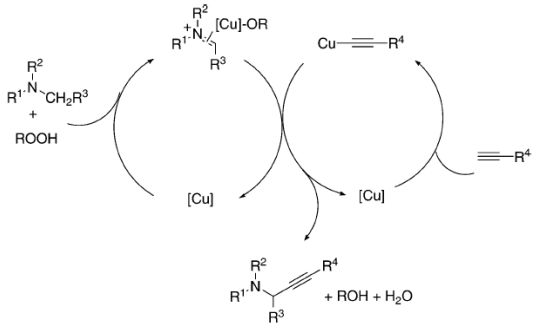
Scheme 3. Reaction of Cyclic Benzylamine



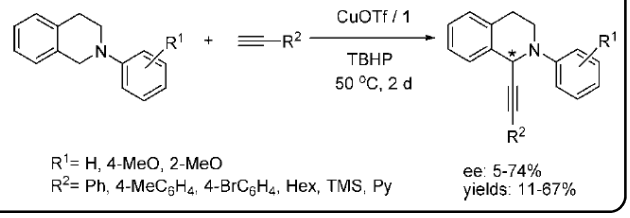
Scheme 4. Reaction of Simple Cyclic Amine



Scheme 5. Tentative Mechanism for the Direct Oxidative Coupling of Amine with Alkyne

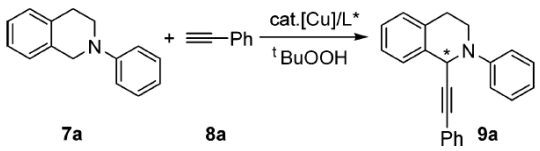


SCHEME 6. Asymmetric Alkynylation of Tetrahydroisoquinolines with Terminal Alkynes



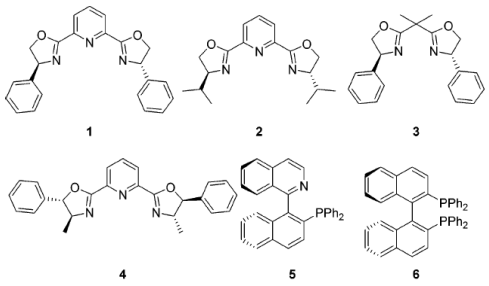
Chao-Jun Li, ***Org. Lett.***, *Vol. 6*, No. 26, **2004**

Table 1. Effect of Conditions on the Enantioselectivity of Coupling of *N*-Benzene Tetrahydroisoquinoline with Phenylacetylene via sp^3 C−H Bond Activation[a]



entry	catalyst	ligand	temp (°C)	solvent[b]	ee[c] (%)
1	CuOTf	**1**	80	no	19
2	CuOTf	**1**	80	toluene	21
3	CuOTf	**1**	50	toluene	42
4	CuOTf	**1**	50	1,2-dichloroethane	20
5	CuOTf	**1**	50	H_2O	18
6	CuOTf	**1**	50	1,4-dioxane	50
7	CuOTf	**1**	50	THF	56
8	CuBr	**1**	50	1,4-dioxane	18
9	$CuBr_2$	**1**	50	1,4-dioxane	12
10	$Cu(OTf)_2$	**1**	50	1,4-dioxane	40
11	CuOTf	**2**	50	dichloromethane	9
12	CuOTf	**3**	50	THF	14
13	CuOTf	**4**	50	THF	13
14	CuOTf	**5**	50	THF	20
15	CuBr	**5**	50	THF	4
16	CuOTf	**6**	50	THF	8
17	**CuOTf**	**1**	**50**	**THF**	**63**[d]

[a] 0.1 mmol of tetrahydroisoquinoline, 0.1 mmol of phenylacetylene, 0.01 mmol of copper salt, 0.015 mmol of ligand, and 0.1 mmol of ^{t}BuOOH (5−6 M in decane); reaction time is 2 days. [b] Solvents were used without distillation, except THF was distilled from sodium. [c] Enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 95/5 hexane/isopropyl alcohol as eluent or 100 hexane. [d] Ca. 50 mg of 4 Å molecular sieves was used.



Scheme 3. Asymmetric Strategies to C_1-Substituted Tetrahydroisoquinolines

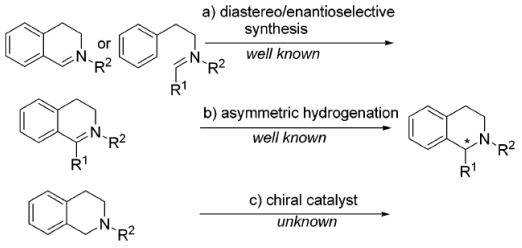
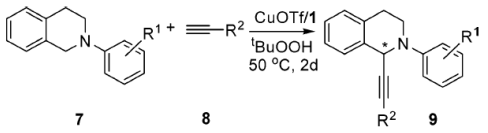


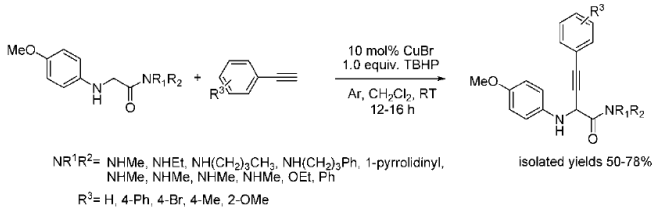
Table 2. Enantioselectivity of Coupling of Tetrahydroisoquinolines with Terminal Alkynes[a]



entry	R^1	R^2	compd	yield[b] (%)	ee[c] (%)
1	H	Ph	**9a**	67	63
2	H	4-MeOPh	**9b**	65	41
3	H	4-BrPh	**9c**	72	64
4	H	Hex	**9d**	65	26
5	H	TMS	**9e**	11	30
6	4-MeO	Ph	**9f**	59	60
7	4-MeO	Hex	**9g**	48	5
8	2-MeO	Ph	**9h**	54	73
9	2-MeO	4-MeOPh	**9i**	56	69
10	2-MeO	4-BrPh	**9j**	61	74
11	2-MeO	Py	**9k**	57	36

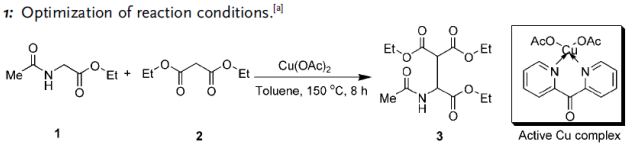
[a] 0.4 mmol of tetrahydroisoquinoline, 0.2 mmol of alkyne, 0.02 mmol of copper salt, 0.03 mmol of ligand, and 0.2 mmol of ^{t}BuOOH (5−6 M in decane). [b] Isolated yields were based on alkynes. [c] Enantiomeric excess was determined with HPLC by using a chiralcel OD-H column and 95/5 hexane/isopropyl alcohol or 100 hexane as eluent.

SCHEME 7. Direct Alkynylation of Glycine Amides via CDC Reaction



Chao-Jun Li, ***Angew. chem. int. Ed.*** **2008**, *47*, 7075-7078

Table 1: Optimization of reaction conditions.[a]

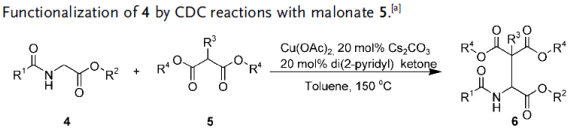


1 2 3

Entry	Ligand	Base	$Cu(OAc)_2$ [equiv]	Yield [%][b]
1	none	none	2.0	5
2	4,4′-dimethyl-2,2″-bipyridine	none	2.0	30
3	1,10-phenanthroline	none	2.0	12
4	TMEDA	none	2.0	23
5	di(2-pyridyl) ketone	none	2.0	56
6	di(2-pyridyl) ketone	NaOAc	2.0	70
7	di(2-pyridyl) ketone	$KHCO_3$	2.0	71
8	di(2-pyridyl) ketone	Cs_2CO_3	2.0	84
9[c]	di(2-pyridyl) ketone	Cs_2CO_3	0.2	15
10[d]	di(2-pyridyl) ketone	Cs_2CO_3	0.2	15
11	di(2-pyridyl) ketone	Cs_2CO_3	1.2	68

[a] Reaction conditions: **1** (0.125 mmol), **2** (0.25 mmol), 20 mol% ligand, 20 mol% base in toluene (1 mL), 150°C, 8 h. [b] Yields were based on compound **1** and determined by NMR spectroscopy using an internal standard. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [c] 5 mol% $Pd(OAc)_2$ was added and run under 1 atm O_2. [d] 5 mol% $Pd(OAc)_2$ was added.

Table 2: Functionalization of **4** by CDC reactions with malonate **5**.[a]

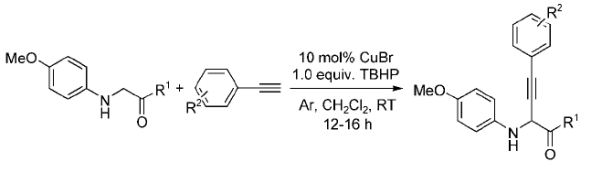


4 5 6

Entry	Reaction *t* [h]	R^1	R^2	R^3	R^4	6[b]	Yield [%][c]
1	6	Me	*i*Pr	H	Et	**6a**	82(73)
2	10	Me	*i*Pr	H	Me	**6b**	85(40)
3	6	Me	*i*Pr	H	*i*Pr	**6c**	80(62)
4	10	Me	*i*Pr	Me	Et	**6d**	94(48)
5	8	Me	Et	H	Et	**6e**	84(72)
6	10	Me	Et	Me	Me	**6f**	75(48)
7	6	Me	Et	H	*i*Pr	**6g**	73(63)
8	6	Me	Et	H	Me	**6h**	63(46)
9	10	Me	Et	Me	Et	**6i**	75(32)
10	6	Me	Me	H	Et	**6j**	65(55)
11	10	Et	Et	Me	Et	**6k**	75
12	10	*i*Pr	Et	Me	Et	**6l**	53
13	10	*t*Bu	Et	Me	Et	**6m**	NR
14	10	Et	Et	Me	Me	**6n**	78
15	10	*i*Pr	Et	Me	Me	**6o**	60
16	10	*t*Bu	Et	Me	Me	**6p**	NR

[a] Reaction conditions: **4** (0.125 mmol), **5** (0.25 mmol), $Cu(OAc)_2$ (0.25 mmol), Cs_2CO_3 (0.025 mmol), di(2-pyridyl) ketone (0.025 mmol), toluene (1 mL). [b] For full experimental data, see the Supporting Information. [c] Yields of isolated product are based on **4**, and the yields after 4 h reaction are given in parentheses. NR = No reaction.

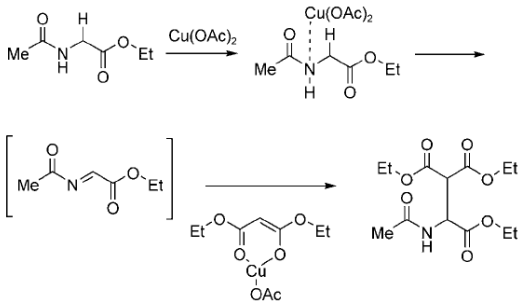
Table 3: Functionalization of **7** by CDC reaction with alkyne **8**.[a]



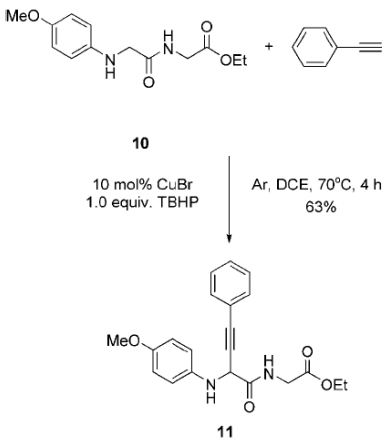
7 8 9

Entry	R^1	R^2	9[b]	Yield [%][c]
1	NHMe	H	**9a**	68(93)
2	NHEt	H	**9b**	55(73)
3	$NH(CH_2)_3CH_3$	H	**9c**	62(79)
4	$NH(CH_2)_3Ph$	H	**9d**	76(93)
5	1-pyrrolidinyl	H	**9e**	67(90)
6	NHMe	4-Ph	**9f**	72(86)
7	NHMe	4-Br	**9g**	78(89)
8	NHMe	4-Me	**9h**	60(81)
9	NHMe	2-OMe	**9i**	50(63)
10	OEt	H	NA	NR
11	Ph	H	NA	ND

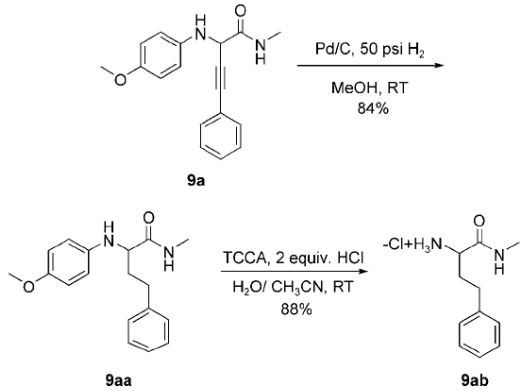
[a] Reaction conditions: **7** (0.30 mmol), **8** (0.90 mmol), TBHP (54 μL, 5–6 M in decane), CuBr (0.03 mmol), CH_2Cl_2 (0.5 mL). [b] For full experimental data, see the Supporting Information [c] Yields of isolated product are based on **7**, and NMR yields, using an internal standard, are given in parentheses. NA = Not applicable. NR = No reaction. ND = Not determined.



Scheme 2. Proposed mechanism for the oxidative functionalization of glycine derivatives with diethyl malonate.



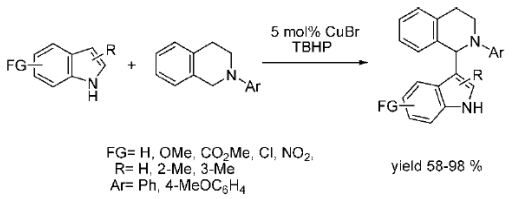
Scheme 3. Functionalization of simple peptide **10** with ethynylbenzene.



Scheme 4. Synthesis of homophenylalanine derivative **9ab**. TCCA = Trichloroisocyanuric acid

Arylation (sp^3-sp^2 Coupling).

SCHEME 10. CDC Reactions of Various Indoles with Tetrahydroisoquinolines

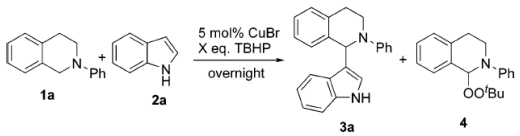


FG= H, OMe, CO_2Me, Cl, NO_2,
R= H, 2-Me, 3-Me
Ar= Ph, 4-$MeOC_6H_4$

yield 58-98 %

Chao-Jun Li, ***J. AM. CHEM. SOC.* 2005,** *127*, 6968-6969

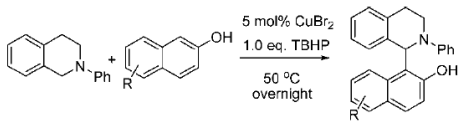
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	T (°C)	2a (equiv)	TBHP (equiv)	conv. of 1a (%)[b]	3a (%)[b]	4 (%)[b]
1	neat	22	1.0	1.0	90	45	<5
2	neat	22	2.0	1.0	85	40	trace
3	neat	50	1.0	1.0	90	75	N.D.[c]
4	neat	50	1.0	1.25	95	70	N.D.[c]
5	*t*-BuOH	50	1.0	1.0	90	30	trace
6[d]	neat	50	1.0	1.0	90	60	N.D.[c]
7	neat	50	1.5	1.5	100	60	N.D.[c]
8	H_2O/PhMe (0.5 mL/0.1 mL)	50	1.2	1.3	100	50	N.D.[c]
9	H_2O/PhMe (2.0 mL/1.0 mL)	50	1.2	1.3	100	N.D.[c]	70
10	neat	50	1.2	1.3	100	85	N.D.[c]

[a] Tetrahydroisoquinoline (0.1 mmol) was used; unless otherwise noted; ^{t}BuOOH (5−6 M in decane). [b] Detected by NMR using an internal standard. [c] Not detected by NMR. [d] Tetrahydroisoquinoline (0.15 mmol) was used.

SCHEME 11. CDC Reaction of Tetrahydroisoquinoline with 2-Naphthol Derivatives

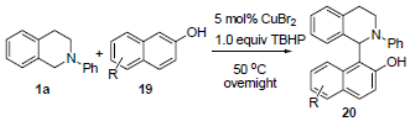


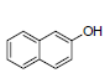
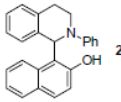
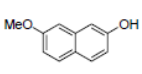
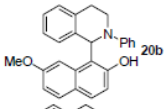
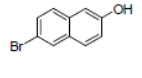
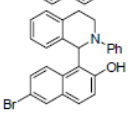
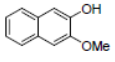
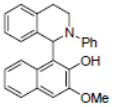
R= H, 3-OMe, 6-OMe, 7-Br

yield, 49-63%

Chao-Jun Li, ***PANS* 2006**, *103,* 8928-8933

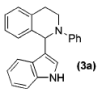
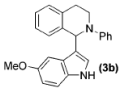
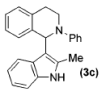
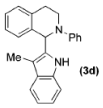
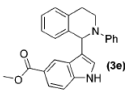
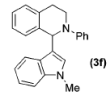
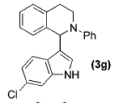
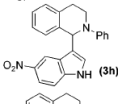
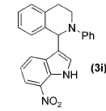
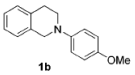
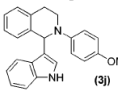
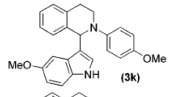
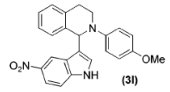
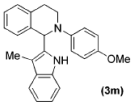
Table 8. CDC Reaction of Tetrahydroisoquinoline with 2-Naphthol Derivatives[a]



entry	19	product 20		yield[b]
1			20a	72 (53)
2			20b	74 (63)
3			20c	61 (49)
4			20d	69 (55)

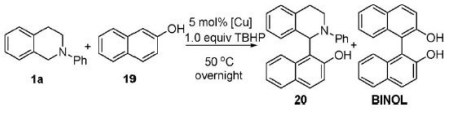
[a]Tetrahydroisoquinoline (0.2 mmol), 2-naphthol derivatives (0.1 mmol), TBHP (0.2 mmol, 5.5 M in decane), and $CuBr_2$ (5 mol%). [b] NMR yields are based on 2-naphthol derivatives and determined by ^{1}H NMR using an internal standard; isolated yields are given in parentheses.

Table 2. CDC Reaction of Indoles with Tetrahydroisoquinolines[a]

entry	1	2	product	yield (%)[b]
1	 1a	 2a	 (3a)	86 (79)
2	1a	 2b	 (3b)	89 (57)
3	1a	 2c	 (3c)	80 (61)
4	1a	 2d	 (3d)	81 (77)
5	1a	 2e	 (3e)	77 (63)
6	1a	 2f	 (3f)	58 (44)
7	1a	 2g	 (3g)	89 (73)
8	1a	 2h	 (3h)	(85)
9	1a	 2i	 (3i)	64 (50)
10	 1b	2a	 (3j)	95 (71)
11	1b	2b	 (3k)	98 (65)
12	1b	2h	 (3l)	78 (50)
13	1b	2d	 (3m)	95 (49)

[a] Tetrahydroisoquinolines (0.1 mmol), indoles (0.12 mmol), CuBr (0.005 mmol, 5 mol %), and ^{t}BuOOH (0.13 mmol, 5−6 M in decane). [b] NMR yields are based on tetrahydroisoquinolines and determined by NMR using an internal standard; isolated yields are given in parentheses.

Table 7. CDC reaction of tetrahydroisoquinoline with 2-naphthol

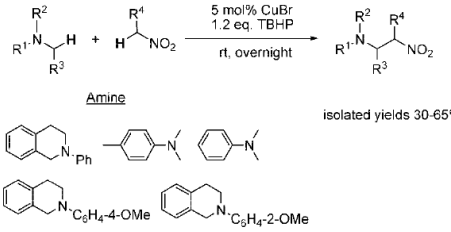


Entry	[Cu]	Yield of 20*	Yield of BINOL*
1	CuI	57	13
2	CuCl	51	10
3	CuBr	58	23
4	$CuBr_2$	63	10
5†	CuBr	63	10
6†	$CuBr_2$	72	11
7	$CuSO_4$	53	11
8	$Cu(OTf)_2$	55	15

Tetrahydroisoquinoline (0.1 mmol), 2-naphthol (0.1 mmol), TBHP (0.1 mmol, 5.5 M in decane), and [Cu] (5 mol%): otherwise are mentioned.
*Reported yields were NMR yields using an internal standard.
†Tetrahydroisoquinoline (0.2 mmol).

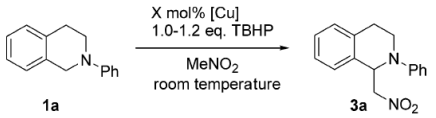
Alkylation (sp^3-sp^3).

SCHEME 12. CDC Reaction of Tertiary Amines with Nitroalkanes



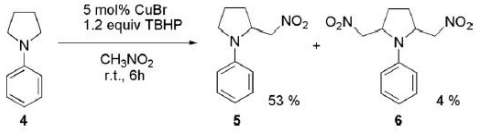
Chao-Jun Li, ***J. AM. CHEM. SOC.*** **2005,** *127*, 3672-3673

Table 1. Optimization of Reaction Conditions[a]



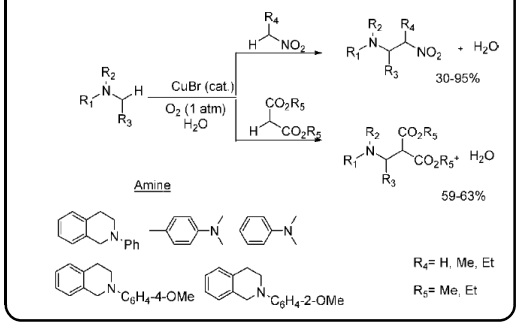
entry	catalyst	X mol %	reaction time (NMR yield%)[b]
1	CuCl	10	3 h (70); 6 h (75)
2	CuBr	10	3 h (90)
3	CuI	10	3 h (60); 6 h (80)
4	CuOTf	10	3 h (20); 6 h (50)
5	$CuCl_2$	10	3 h (60); 6 h (80)
6	$CuBr_2$	10	3 h (40); 6 h (92)
7	$Cu(OTf)_2$	10	3 h (5); 6 h (35)
8	$Cu(OAc)_2 \cdot H_2O$	10	3 h (50); 6 h (80)
9[c]	CuBr	5	6 h (92)
10[d]	CuBr	2	3 h (60); 6 h (90)
11	no	0	3 h (0)

[a] 0.1 mmol tetrahydroisoquinoline, 1.0 mL of nitromethane, and 0.02 mL of ^{t}BuOOH (5−6 M in decane). [b] Reported yields were based on tetrahydroisoquinoline and determined by NMR using an internal standard. [c] 0.2 mmol tetrahydroisoquinoline, 1.0 mL of nitromethane, and 0.04 mL of ^{t}BuOOH (5−6 M in decane). [d] 0.5 mmol tetrahydroisoquinoline, 2.0 mL of nitromethane, and 0.1 mL of ^{t}BuOOH (5−6 M in decane).



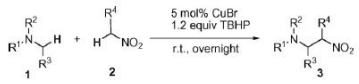
Scheme 2. Reaction of 1-phenylpyrrolidine with nitromethane.

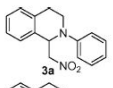
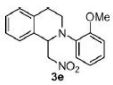
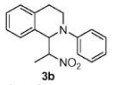
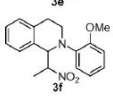
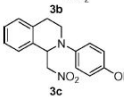
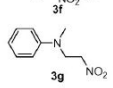
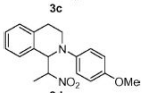
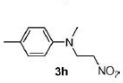
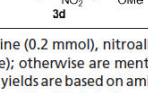
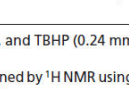
SCHEME 15. CDC Reaction of Tertiary Amines with Oxygen in Water



Chao-Jun Li, ***Green Chem*****, 2007,** *9,* 1047-1050

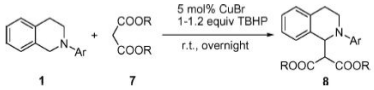
Table 1. CDC reaction of tertiary amines with nitroalkanes

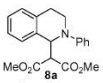
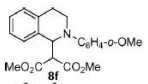
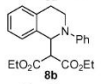
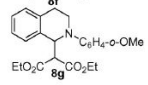
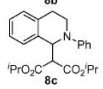
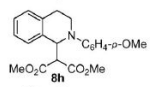
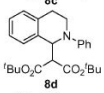
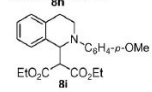
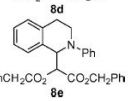


Entry	Product	Yields (%)*	Entry	Product	Yields (%)*
1	 3a	84(65)	6	 3e	76(62)
2†	 3a	70(61)	7†	 3e	70(60)
3†	 3b	69(52)	8†	 3f	77(51)
4	 3c	80(61)	9§	 3g	(30)
5‡	 3d	81(56)	10§	 3h	(62)

Amine (0.2 mmol), nitroalkane (0.4 mmol), and TBHP (0.24 mmol, 5.5 M in decane); otherwise are mentioned.
*NMR yields are based on amines and determined by ^{1}H NMR using an internal standard; isolated yields are given in parentheses.
†1 equiv (0.2 mmol) of nitromethane was used.
‡The ratio of two isomers is 2.1.
§1 ml of nitromethane was used.

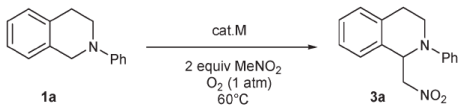
Table 2. CDC reaction of tertiary amines with malonates



Entry	Product	Yields (%)*	Entry	Product	Yields (%)†
1	 8a	74	7	 8f	71
2†	8a	72			
3	 8b	65	8	 8g	56
4	 8c	82	9†	 8h	70
5	 8d	78	10	 8i	58
6	 8e	70			

Tetrahydroisoquinoline (0.1 mmol), malonate (0.1 mmol), and TBHP (0.02 ml, 5–6 M in decane). [Reproduced with permission from ref. 25 (Copyright 2005, Wiley).]
*Isolated yields.
†CuBr (0.005 mmol, 0.5 mol%), tetrahydroisoquinoline (1.0 mmol), malonate (1.0 mmol), and TBHP (0.2 ml, 5–6 M in decane); the reaction time is 43 h.
‡Malonate (0.2 mmol).

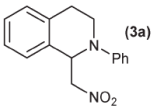
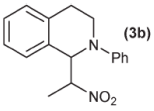
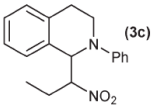
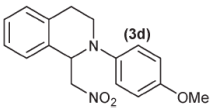
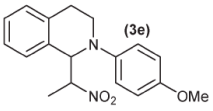
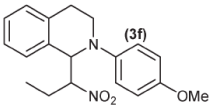
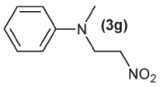
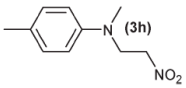
Table 1 Optimization of reaction conditions[a]



Entry	Solvent	$RuCl_3$ (mol%)	CuBr (mol%)	Time/h	Yield[b]
1	H_2O	5	0	18	45
2	H_2O	10	0	18	67
3	H_2O	5	1	18	62
4	H_2O	5	2	18	73
5	H_2O	5	5	18	90
6	H_2O	0	5	16	90
7	MeOH	0	5	16	90

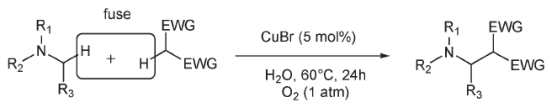
[a] Tertiary amine (0.2 mmol) and nitroalkane (0.4 mmol) were stirred under O_2 (1 atm) at 60 °C in 0.6 mL of water. [b] NMR yields based on tetrahydoisoquinoline using an internal standard.

Table 2 Catalytic CDC reactions between tertiary amines with nitroalkanes with oxygen in water[a]

Entry	Nitroalkanes	T/°C	Products	Yield (%)[d]
1	$MeNO_2$ **2a**	60	 **(3a)**	90 (79)[b]
2	$EtNO_2$ **2b**	60	 **(3b)**	90 (75)
3	$PrNO_2$ **2c**	60	 **(3c)**	95 (82)
4	**2a**	40	 **(3d)**	95 (72)[b]
5	**2b**	40	 **(3e)**	80 (67)
6	**2c**	40	 **(3f)**	85 (69)
7	**2a**	60	 **(3g)**	(30)[c]
8	**2a**	60	 **(3h)**	75 (63)[c]

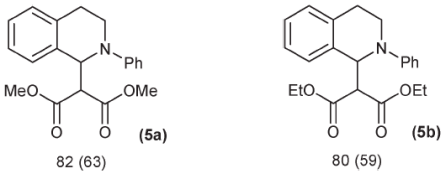
[a] Tertiary amine (0.2 mmol), nitroalkane (1 mmol), CuBr (5 mol%), under O_2 (1 atm) at 60 °C for 16 h in 0.6 mL of water. [b] Nitromethane (0.2 mmol) was use. [c] Nitromethane (1.0 mL, 92 equiv) was use. [d] NMR yields based on tertiary amines with an internal standard (isolated yield are given in parentheses).

Table 3 CDC reaction of tetrahydroisoquinoline with malonate[a]



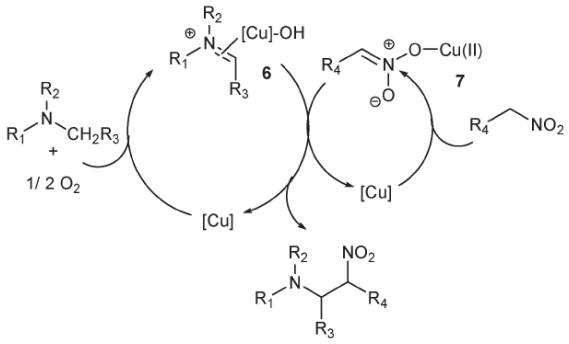
1 4 3

Products (isolated yields %)[b]



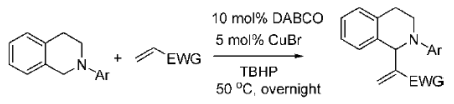
82 (63) 80 (59)

[a] Terahydoisoquinoline (0.2 mmol) and malonate (0.2 mmol) under O_2 at 60 °C for 24 h in water. [b] NMR yields based on tertiary amines with an internal standard (isolated yield are given in parantheses).



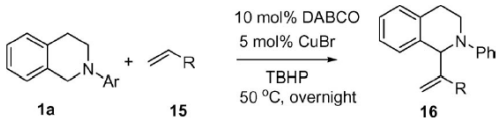
Scheme 2 Possible mechanism.

SCHEME 16. Aza-Baylis–Hillman-type CDC Reaction



Chao-Jun Li, ***PANS* 2006**, *103*, 8928-8933

Table 5. Aza–Baylis–Hillman type CDC reaction

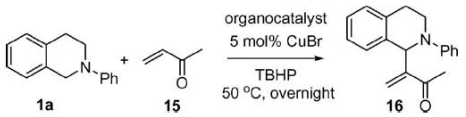


1a 15 16

Entry	Ar	R	Product	Yield, %*
1	Ph	Acyl	**16a**	53 (30)
2	Ph	CN	**16b**	61 (58)
3	4-$MeOC_6H_4$	Acyl	**16c**	31 (29)
4	4-$MeOC_6H_4$	CN	**16d**	74 (69)

Tetrahydroisoquinoline (0.2 mmol), alkene (0.4 mmol), TBHP (0.2 mmol, 5.5 M in decane), CuBr (5 mol%), DABCO (10 mol%), and 4-Å molecular sieve (60 mg). *NMR yields are based on tetrahydroisoquinoline and determined by ^{1}H NMR using an internal standard; isolated yields are given in parentheses.

Table 4. CDC reaction of tetrahydroisoquinoline with MVK



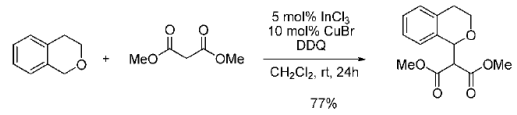
1a 15 16

Entry	Organocatalyst	Temperature, °C	Yield, %*
1	PPh_3, 30 mol%	RT	10
2	PPh_3, 30 mol%	50	20
3	DABCO, 5 mol%	50	30
4	DABCO, 30 mol%	50	28
5	DABCO, 10 mol%	RT	24
6†	DABCO, 10 mol%	50	53

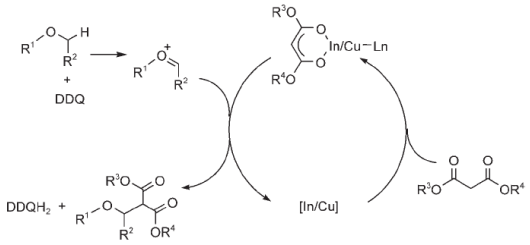
Tetrahydroisoquinoline (0.1 mmol). Methylvinylketone (MVK) (0.2 mmol). TBHP (0.1 mmol, 5.5 M in decane), and CuBr (5 mol%).
*Reported yields were based on tetrahydroisoquinoline and determined by ^{1}H NMR using an internal standard.
†4-Å molecular sieve (30 mg) was added.

CDC Reaction of ¦Á-C-H Bonds of Oxygen in Ethers (sp^3-sp^3)

SCHEME 17. CDC Reaction of Isochroman with Dimethyl Malonate

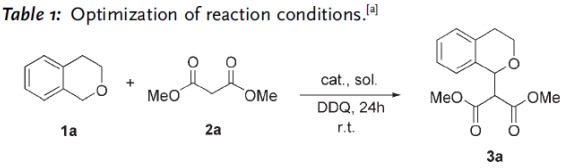


Chao-Jun Li, *Angew. Chem. Int. Ed.* **2006,** *45,* 1949-1952



Scheme 3. Possible mechanism for the CDC reaction of ether with malonate.

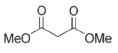
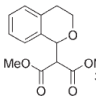
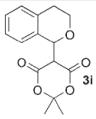
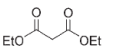
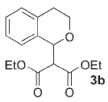
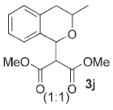
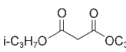
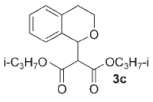
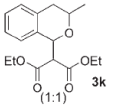
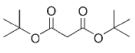
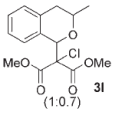
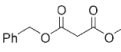
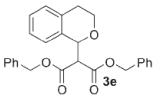
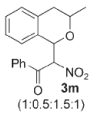
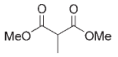
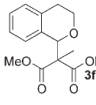
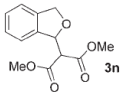
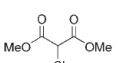
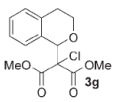
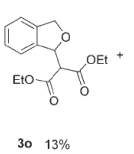
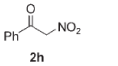
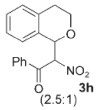
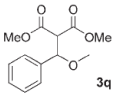
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Conversion (**1a**) [%][b]	Yield (**3a**) [%][b]
1	$InCl_3$[c]	CH_2Cl_2	96	72
2	$In(OAc)_3$[c]	CH_2Cl_2	100	n.d.[d]
3	$In(OTf)_3$[c]	CH_2Cl_2	94	76
4	$In(NO_3)_3$[c]	CH_2Cl_2	100	n.d.[d]
5	$In(OH)_3$[c]	CH_2Cl_2	100	n.d.[d]
6	$Cu(OTf)_2$[c]	CH_2Cl_2	93	69
7	Cu(OTf)[c]	CH_2Cl_2	94	50
8	$InCl_3/Cu(OTf)_2$ (5 mol%/5 mol%)	CH_2Cl_2	92	77
9	$InCl_3/Cu(OTf)_2$ (10 mol%/5 mol%)	CH_2Cl_2	95	74
10	$InCl_3/Cu(OTf)_2$ (5 mol%/10 mol%)	CH_2Cl_2	95	77
11	$InCl_3/Cu(OTf)$[e]	CH_2Cl_2	96	71
12	$InCl_3/Cu(OTf)_2$[e]	DCE	96	76
13	$InCl_3/Cu(OTf)_2$[e]	$MeNO_2$	82	66
14	$InCl_3/Cu(OTf)_2$[e]	THF	0	n.d.[d]
15	$InCl_3/Cu(OTf)_2$[e]	H_2O	68	n.d.[d]
16	$InCl_3/Cu(OTf)_2$[e]	PhMe	80	43
17	$InCl_3/Cu(OTf)_2$[e]	MeCN	68	44

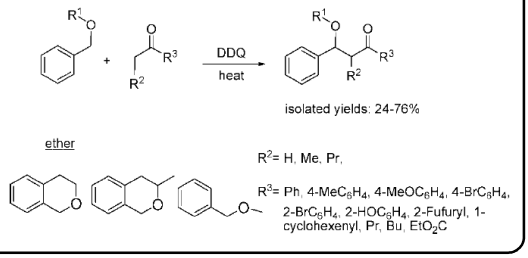
[a] Isochroman (0.5 mmol), dimethyl malonate (0.6 mmol), DDQ (0.6 mmol), solvent (2–3 mL). [b] Determined by ^{1}H NMR spectroscopy using an internal standard. [c] Catalyst: 10 mol%. [d] Not detected by ^{1}H NMR spectroscopy. [e] In/Cu (5 mol%/5 mol%).

Table 2: CDC reaction of ethers with active methylene compounds.[a]

Entry	1	2	Product	Yield [%][b]	Entry	1	2	Product	Yield [%][b]
1	 **1a**	 **2a**	 **3a**	71	9	**1a**	 **2i**	 **3i**	65
2	**1a**	 **2b**	 **3b**	66	10	 **1b**	**2a**	 **3j** (1:1)	60
3	**1a**	 **2c**	 **3c**	63	11	**1b**	**2b**	 **3k** (1:1)	57
4	**1a**	 **2d**	decomp.		12	**1b**	**2g**	 **3l** (1:0.7)	40
5	**1a**	 **2e**	 **3e**	65	13	**1b**	**2h**	 **3m** (1:0.5:1.5:1)	65
6	**1a**	 **2f**	 **3f**	53	14[c]	 **1c**	**2a**	 **3n**	48
7	**1a**	 **2g**	 **3g**	64	15[d]	**1c**	**2b**	 **3o** 13% + **3p** 15% (1.5:1)	
8	**1a**	 **2h**	 **3h** (2.5:1)	72	16	 **1d**	**2a**	 **3q**	17

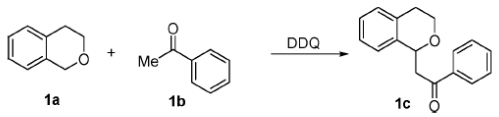
[a] Diethyl ether (0.5 mmol), active methylene compound (0.6 mmol), $InCl_3/Cu(OTf)_2$ (5 mol%/5 mol%), DDQ (0.6 mmol); all reactions were run for 24–36 h. [b] Yields of isolated products based on ethers. [c] Phthalan (0.2 mmol), dimethyl malonate (0.4 mmol), DDQ (0.2 mmol). [d] Phthalan (0.2 mmol), diethyl malonate (0.4 mmol), DDQ (0.24 mmol).

SCHEME 18. CDC Reaction between Benzyl Ethers and Simple Ketones



Chao-Jun Li, ***J. AM. CHEM. SOC.* 2006**, *128,* 4242-4243

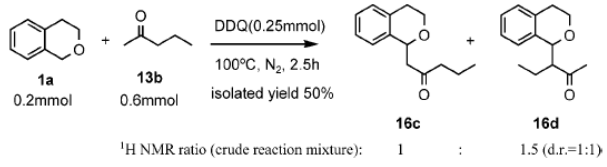
Table 1. CDC Reaction of Isochroman with Acetophenone[a]



entry	ether/ketone/DDQ (mmol)	solvent[b]	temp (°C)	yield (%)[c]
1[d]	0.2/0.4/0.24	$[BMIM]PF_6$	rt	5
2[e]	0.2/0.4/0.24	neat	rt	nd[f]
3	0.2/0.4/0.24	neat	50	10
4	0.2/0.4/0.24	CH_2Cl_2	reflux	nd[f]
5	0.2/0.4/0.24	1,4-dioxane	reflux	nd[f]
6[g]	0.2/0.4/0.24	DMSO	100	nd[f]
7	0.2/0.4/0.24	PhMe	reflux	40
8	0.2/0.4/0.24	$MeNO_2$	reflux	60
9	0.2/0.4/0.24	H_2O	reflux	45
10	0.2/0.4/0.24	DCE	reflux	38
11	0.2/0.4/0.24	THF	reflux	10
12	0.2/0.4/0.24	hexane	reflux	10
13	0.2/0.4/0.24	MeCN	reflux	35
14	0.2/0.4/0.24	neat	100	76
15	0.2/0.4/0.24	neat	125	71
16[h]	0.4/0.2/0.24	neat	100	37
17	0.2/0.4/0.2	neat	100	66
18	0.2/0.4/0.3	neat	100	62

[a] Reaction time: 2 h. [b] Solvent (0.5 mL) was used. [c] ^1H NMR yield using an internal standard. [d] Reaction time: overnight, $InCl_3/Cu(OTf)_2$ a catalyst. [e] Reaction time: overnight. [f] Not detected by ^1H NMR. [g] Isoch roman (60%) remained after the reaction. [h] Yield was based on ketone.

Scheme 2. CDC Reaction of Isochroman with 2-pentanone



Scheme 3. Tentative Mechanism for the CDC Reaction of Benzyl Ethers with Ketones Mediated by DDQ

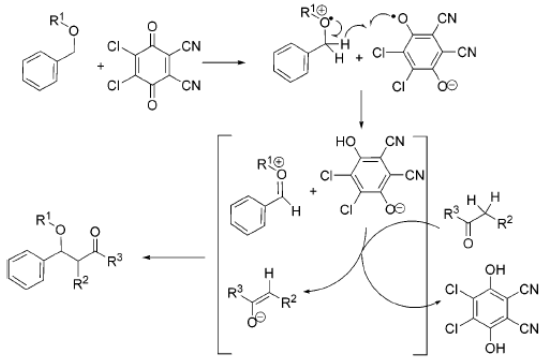


Table 2. CDC Reaction of Benzyl Ethers with Ketones[a]

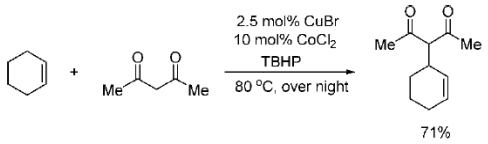
entry	ether	ketone	product	yield(%)[b]
1	1a	1b	1c	69 (78)[c]
2	1a	2b	2c	75 (86)[c] (1:1)
3	1a	3b	3c	65
4	1a	4b	4c	68
5	1a	5b	5c	53
6	1a	6b	6c	60
7	1a	7b	7c	30
8	1a	8b	8c	69
9	1a	9b	9c	39
10	1a	10b	10c	76 (1:1)
11	1a	11b	11c	60 (1:1)
12	1a	12b	12c	40
13	2a	10b	13c	65 (1:1:0.8:1.2)
14	3a	2b	14c	59 (1:1)
15	3a	10b	15c	24 (1:2)

[a] Reaction conditions: ether (0.2mmol), ketone (0.6 mmol), DDQ (0.24 mol), N_2, 100 °C, 2.5 h. [b] Isolated yield; the ratios of diastereomers easured prior to purification are given in parentheses. [c] ^1H NMR yield ith internal standard.

CDC Reaction of Allylic and Benzylic C-H Bonds

Allylic Alkylation (sp^3-sp^3).

SCHEME 21. Allylic Alkylation via CDC Reaction



Chao-Jun Li, ***J. AM. CHEM. SOC.*** **2006**, *128*, 56-57

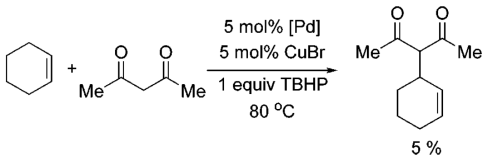
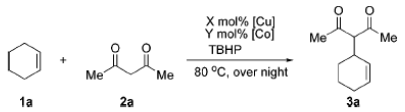
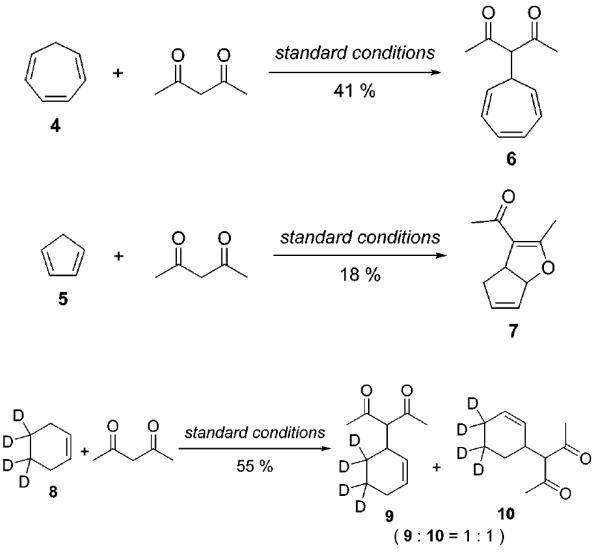


Table 1. Optimization of Reaction Conditions



entry	1a (mmol)	2a (mmol)	[Cu][a] (mol %)	[Co][a] (mol %)	TBHP (mmol)	yield (%)[c]
1	2.5	1.0	5	5	1.0	25
2	2.5	1.0	5	2.5	2.0	12
3	1.0	2.0	5	5	1.0	6
4	2.5	1.0	5	10	1.0	36
5	2.5	1.0	10	10	1.5	29
6	5.0	1.0	1	10	2.0	62
7	5.0	1.0	2.5	10	2.0	71
8	5.0	1.0	1.25	5	2.0	60
9	5.0	1.0	2.5 (CuI)	10	2.0	57
10	5.0	1.0	2.5 ($CuBr_2$)	10	2.0	60
11	5.0	1.0	2.5 (CuCl)	10	2.0	70
12	5.0	1.0	2.5	10 (CoI_2)	2.0	10
13	5.0	1.0	2.5	10 (CoF_2)	2.0	trace
14	2.5	1.0	0	5	1.0	10
15	2.5	1.0	5	0	1.0	0

[a] CuBr was used, unless otherwise noted. [b] $CoCl_2$ was used, unless otherwise noted. [c] NMR yields using an internal standard.



SCHEME 20. Tsuji–Trost Reaction and Allylic CDC Reaction

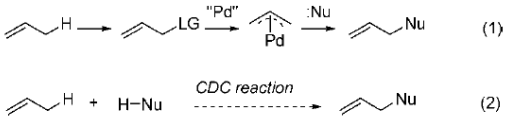
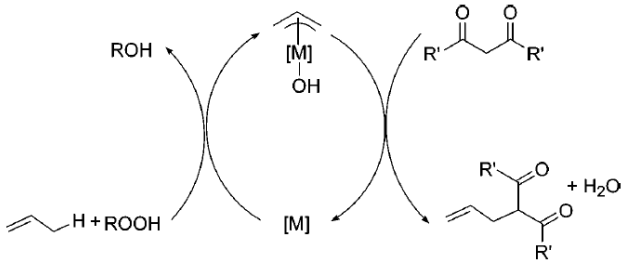


Table 2. Cross-Dehydrogenative-Coupling Reactions of Allylic C–H and β-Dicarbonyl C–H[a]

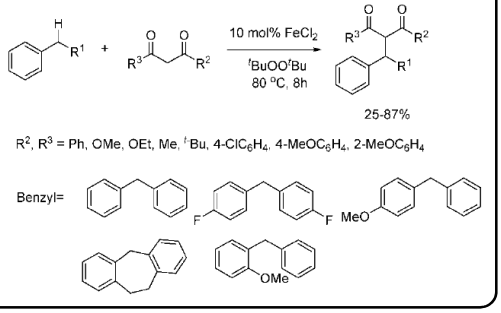
Entry	Alkene	Diketone	Product	Yield (%)[b]
1	1a	2b	3b	61
2	1a	2c	3c	64 (1:1)
3	1a	2d	3d	41 (1:1)
4	1a	2e	3e	71 (1:1)
5	1a	2f	3f	55 (1:1)
6	1a	2g	3g	31 (1:1)
7	1a	2h	3h	46 (1.7:1)
8	1a	2i	3i	41
9	1b	2a	3j	34
10	1c	2a	3k	53[c]
11	1d	2a	3l	30
12	1e	2a	3m	35

[a] Conditions: 0.025 mmol of CuBr, 0.1 mmol of $CoCl_2$, 5.0 mmol of alkene, 1.0 mmol of 1,3-dicarbonyl compound, and 2.0 mmol of TBHP. [b] Isolated yields were based on 1,3-dicarbonyl compounds; the ratio of two diastereomers is given in parentheses. [c] At 50 °C.



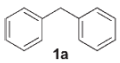
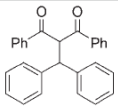
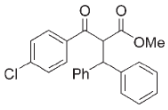
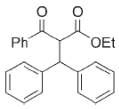
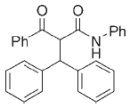
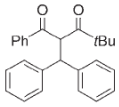
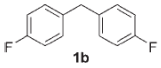
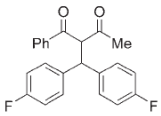
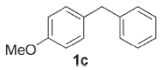
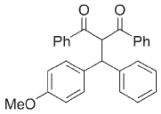
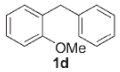
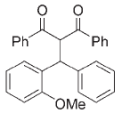
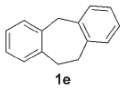
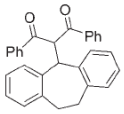
Benzylic Alkylation (sp^3-sp^3).

SCHEME 23. Benzylic Alkylation via CDC

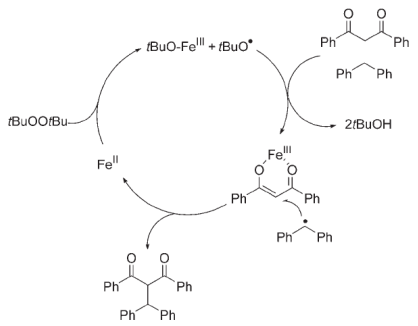


Chao-Jun Li, ***Angew. Chem. Int. Ed.*** **2007**, *46*, 6505-6507

Table 2: Alkylation of diaryl C–H bonds.[a]

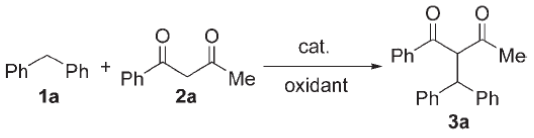
Entry	Diaryl substrate	Product	Yield [%][b]
1	 1a	 3b	68
2	**1a**	 3c	65
3	**1a**	 3d	65
4	**1a**	 3e	84
5	**1a**	 3f	25
6	 1b	 3g	66
7	 1c	 3h	64
8	 1d	 3i	40
9	 1e	 3j	67

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2$ (0.1 mmol), 80°C, 8 h. [b] Yield of isolated product.



Scheme 3. A tentative mechanism for the $FeCl_2$-catalyzed benzylic alkylation.

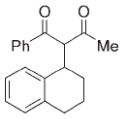
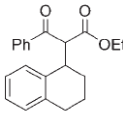
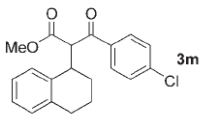
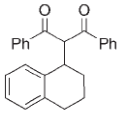
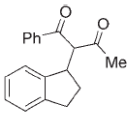
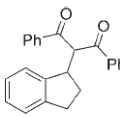
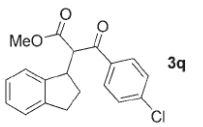
Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Oxidant (equiv)	*T* [°C]	*t* [h]	Yield [%][b]
1	$CoCl_2$ (10)	TBHP (2)	100	5	11
2	$CuBr/CoCl_2$ (10/10)	TBHP (2)	100	5	30
3	CuBr (10)	TBHP (2)	100	5	n.d.[c]
4	$FeCl_2$ (20)	TBHP (2)	80	8	46
5	$FeCl_2$ (20)	*t*BuOO*t*Bu (2)	80	8	66
6	$FeCl_2$ (10)	*t*BuOO*t*Bu (2)	80	8	47
7	$FeCl_2$ (20)	PhCOOO*t*Bu (2)	80	8	n.d.[c]
8	$FeCl_2$ (20)	*t*BuOO*t*Bu (1)	80	8	64
9	$FeBr_2$ (20)	*t*BuOO*t*Bu (2)	80	8	49
10	$FeCl_3$ (20)	*t*BuOO*t*Bu (2)	80	8	56
11	$Fe(OAc)_2$ (20)	*t*BuOO*t*Bu (2)	80	8	n.d.[c]
12[d]	$FeCl_2$ (20)	*t*BuOO*t*Bu (2)	80	8	46
13	$FeCl_2$ (20)	*t*BuOO*t*Bu (1)	RT	36	65
14	$FeCl_2$ (20)	*t*BuOO*t*Bu (2)	RT	36	80
15	–	*t*BuOO*t*Bu (2)	80	8	n.d.[c]

[a] 1-Benzoylacetone (0.5 mmol), diphenylmethane (6.0 mmol), and TBHP (5–6 M in decane) under nitrogen, unless otherwise noted. [b] Yield of isolated product. [c] Not detected by NMR spectroscopy. [d] Only 1.0 mmol of diphenylmethane was used.

Table 3: Alkylation of cyclic benzylic C–H bonds.[a]

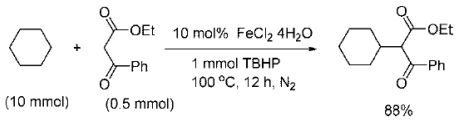
Entry	Cyclic substrate	Product	Yield [%][b]
1	 1f	 3k	71 (1.2:1)
2	**1f**	 3l	87 (1:1)
3	**1f**	 3m	78 (1:1)
4	**1f**	 3n	61
5	 1j	 3o	85 (1.2:1)
6	**1j**	 3p	60
7	**1j**	 3q	80 (1:1)

[a] Conditions: **1** (6.0 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2$ (0.1 mmol), 80°C, 8 h. [b] Yield of isolated product. The ratio of the two diastereomers is given in parentheses.

CDC Reaction of Alkane C-H Bonds

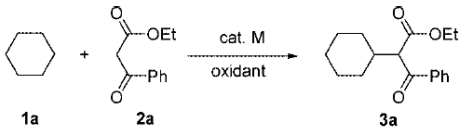
Alkane Alkylation (sp^3-sp^3).

SCHEME 24. Alkane Alkylation via CDC



Chao-Jun Li, ***Eur. J. Org. Chem.*** **2007**, 4654-4657

Table 1. Optimization of reaction conditions.[a]



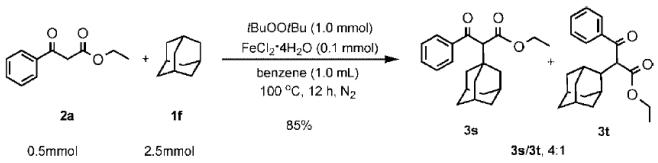
Entry	Catalyst (mol-%)	Oxidant (equiv.)	T [°C]	Yield [%][b]
1[c]	$FeCl_2 \cdot 4H_2O$ (20)	PhC(O)OO*t*Bu (2.0)	100	30
2	$FeCl_2 \cdot 4H_2O$ (20)	TBHP (2.0)	100	N.D.[d]
3	$FeCl_2 \cdot 4H_2O$ (20)	PhC(O)OO*t*Bu (2.0)	100	52
4	$FeCl_2 \cdot 4H_2O$ (20)	Di(*tert*-butylperoxyisopropyl)benzene (1.0)	100	60
5	$FeCl_2 \cdot 4H_2O$ (20)	$PhC(CH_3)_2OOC(CH_3)_2Ph$ (2.0)	100	75
6	$FeCl_2 \cdot 4H_2O$ (20)	$PhC(CH_3)_2OOtBu$ (2.0)	100	75
7	$FeCl_2 \cdot 4H_2O$ (20)	PhC(O)OOC(O)Ph (2.0)	100	35
8	$FeCl_2 \cdot 4H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	79
9	FeF_2 (20)	*t*BuOO*t*Bu (2.0)	100	<5
10	$FeCl_2$ (20)	*t*BuOO*t*Bu (2.0)	100	75
11	$FeBr_2$ (20)	*t*BuOO*t*Bu (2.0)	100	65
12	$FeCl_3$ (20)	*t*BuOO*t*Bu (2.0)	100	65
13	$FeCl_3 \cdot 6H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	70
14	$Fe(NO_3)_3 \cdot 9H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
15	$FeSO_4 \cdot XH_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
16	$Fe(C_2O_4) \cdot 2H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
17	$Fe(acac)_3$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
18	$FeCl_2 \cdot 4H_2O$ (20)	*t*BuOO*t*Bu (2.0)	75	40
19	$FeCl_2 \cdot 4H_2O$ (10)	*t*BuOO*t*Bu (2.0)	100	20
20	$FeCl_2 \cdot 4H_2O$ (20)	*t*BuOO*t*Bu (1.0)	100	54
21	$FeCl_2 \cdot 4H_2O$ (40)	*t*BuOO*t*Bu (2.0)	100	80
22	$FeCl_2 \cdot 4H_2O$ (20)	*t*BuOO*t*Bu (4.0)	100	75
23	----------	*t*BuOO*t*Bu (2.0)	100	<5

[a] Ethyl benzoylacetate (0.2 mmol), cyclohexane (4.0 mmol), 12 h under N_2; unless otherwise noted; TBHP (5–6 M in decane). [b] NMR spectroscopic yields by using an internal standard. [c] Ethyl benzoylacetate (0.2 mmol), cyclohexane (1.0 mL), 12 h. [d] Not detected by NMR spectroscopy.

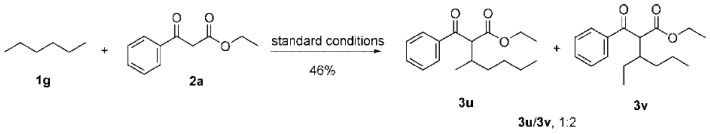
Table 2. $FeCl_2$-catalyzed alkylation of alkane C–H bonds.[a]

Entry	Alkane	Products	Yield [%][b]
1	**1a**	**3a**	88
2	**1a**	**3b**	74
3	**1a**	**3c**	64
4	**1a**	**3d**	75
5	**1a**	**3e**	48
6	**1a**	**3f**	83
7	**1a**	**3g**	84
8	**1a**	**3h**	15
9	**1a**	**3i**	10
10	**1b**	**3j**	75
11	**1b**	**3k**	70
12	**1c**	**3l**	77
13	**1c**	**3m**	76
14[c]	**1d**	**3n**	38
15	**1d**	**3o**	82
16	**1d**	**3p**	72
17	**1e**	**3q**	82 (1:1)
18	**1e**	**3r**	49 (1:1)

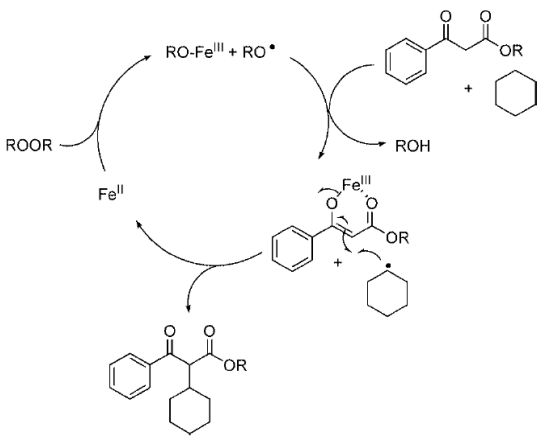
[a] Conditions: **1** (10 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2 \cdot 4H_2O$ (0.1 mmol), 100 °C, 12 h, N_2. [b] Isolated yields are reported; the ratios of two isomers are reported in the parentheses. [c] 23% of **2a** remained after reaction.



Scheme 2. Alkylation of ethyl benzoylacetate with adamantane.



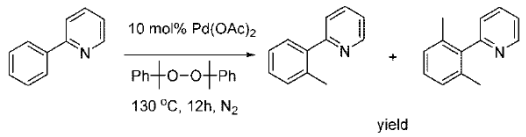
Scheme 3. Alkylation of ethyl benzoylacetate by *n*-hexane.



Scheme 4. Tentative mechanism for the Fe-catalyzed alkylation with simple alkanes.

Alkane Arylation (sp^3-sp^2).

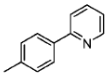
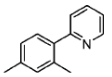
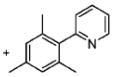
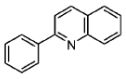
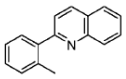
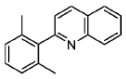
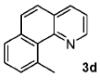
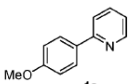
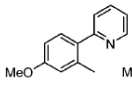
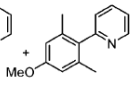
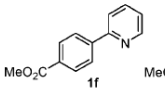
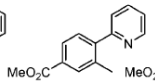
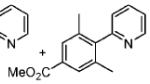
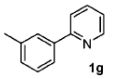
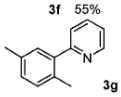
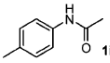
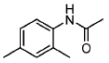
SCHEME 26. Methylation of 2-Phenylpyridine with Dicumyl Peroxide



	yield	
2-phenylpyridine:peroxide = 1 : 1	50%	10%
2-phenylpyridine:peroxide = 1 : 4	0%	70%

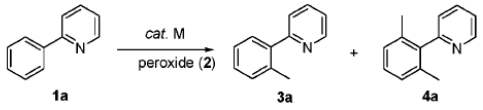
Chao-Jun Li, ***J. AM. CHEM. SOC.*** **2008**, *130,* 2900-2901

Table 2. Methylation of sp^2 C–H Bonds with **2f**[a]

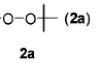
entry	substrate (1)	product and yields[b]		overall yield
				
	1a	3a	4a	
1[c]		54%	18%	72%
2[d]		45%	28%	73%
3[e]			63%	63%
4	3a		55%	55%
5	 1b	 3b 35%	 4b 24%	59%
6	 1c	 3c 55%	 4c 13%(NMR)	68%
7[f]	 1d	 3d		76%
8	 1e	 3e 32%	 4e 28%	60%
9	 1f	 3f 55%	 4f 8%	63%
10	 1g	 3g		63%
11	 1h	 3h		42%
12	 1i	 3i		33%
13	 1j	 3a +  3j	+ 4a	72%
	Total yield of **3a** and **3j** = 42%			30%
	^{1}H NMR ratio of **3a**:**3j** = 1:1			

[a] Conditions: all reactions were carried out with **1** (0.5 mmol), dicumyl peroxide **2f** (1.0 mmol), 12 h under N_2, unless otherwise noted. [b] Isolated yields. [c] **1a** (0.5 mmol), dicumyl peroxide (0.75 mmol). [d] **1a** (0.5 mmol), dicumyl peroxide (1.0 mmol). [e] **1a** (0.5 mmol), dicumyl peroxide (2.0 mmol). [f] **1d** (0.5 mmol), dicumyl peroxide (0.75 mmol).

Table 1. Optimization of Reaction Conditions[a]

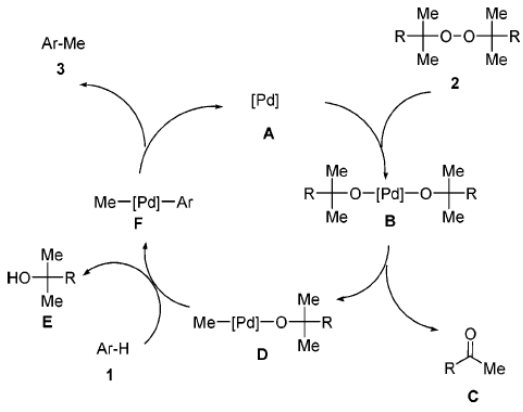


1a **3a** **4a**

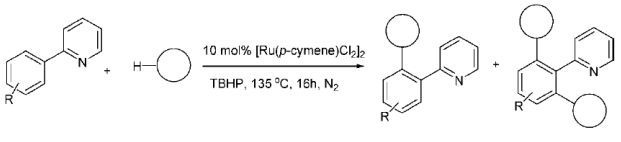
entry	catalyst (mol %)	2 (equiv)		T (°C)	yields of 3 + 4 (%)[b]
1[c]	$Pd(OAc)_2$ (10)	 **(2a)**	(5.0)	140	20 + 0
2[d]	$Pd(OAc)_2$ (10)	**2a**	(5.0)	150	40 + 5
3	$Pd(OAc)_2$ (10)	 **(2b)**	(2.0)	130	0[e]
4	$Pd(OAc)_2$ (10)	PhC(O)O–O– **(2c)**	(2.0)	130	5 + 0[f]
5	$Pd(OAc)_2$ (10)	Ph–O–O– **(2d)**	(2.0)	130	50 + 10
6	$Pd(OAc)_2$ (10)	*p*-C_6H_4–(O–O–)$_2$ **(2e)**	(1.0)	130	50 + 10
7	$Pd(OAc)_2$ (10)	Ph–O–O–Ph **(2f)**	(2.0)	130	50 + 40
8	$PdCl_2$ (10)	**2f**	(2.0)	130	65 + 10
9	$(CH_3CN)_2PdCl_2$ (10)	**2f**	(2.0)	130	55 + 7
10	$Pd(CF_3COO)_2$ (10)	**2f**	(2.0)	130	30 + 10
11	$Pd(PPh_3)_4$ (10)	**2f**	(2.0)	130	30 + 0[f]
12	$Pd(C_5H_7O_2)_2$ (10)	**2f**	(2.0)	130	20 + 5
13	$(PPh_3)_2PdCl_2$ (10)	**2f**	(2.0)	130	20 + 0[f]
14	$Pd(OAc)_2$ (10)	**2f**	(1.0)	130	50 + 10
15	$Pd(OAc)_2$ (10)	**2f**	(4.0)	130	0[f] + 70
16	$Pd(OAc)_2$ (10)	**2f**	(2.0)	150	50 + 45
17	$Pd(OAc)_2$ (10)	**2f**	(2.0)	100	40 + 5
18	$Pd(OAc)_2$ (5)	**2f**	(2.0)	130	60 + 20
19	-------	**2f**	(2.0)	130	0[e]

[a] Conditions: all reactions were carried out with **1a** (0.2 mmol), 12 h under N_2 in a closed reaction vessel, unless otherwise noted. [b] ^{1}H NMR yields determined by using 1,4-dioxane as an internal standard. [c] Reaction time: 5 h. [d] *tert*-Butylbenzene (0.1 mL) as solvent. [e] Not detected by ^{1}H NMR; 90% of **1a** remained. [f] Not detected by ^{1}H NMR.

Scheme 2. Tentative Mechanism for the Palladium-Catalyzed Methylation of Arenes with Peroxides, [Pd] = Pd(0) or Pd(II)



SCHEME 28. CDC Reaction between Phenylpyridines and Cycloalkanes

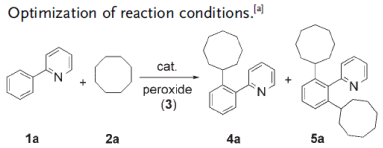


R= H, 4-Me, 4-MeO, 4-F, 4-Ph, 4-EtO$_2$C, 3-Me, 3-F, 3-MeO

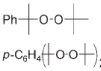
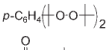
Cycloalkane= cyclohexane, cycloheptane, cyclooctane

total yield 42-75%

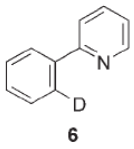
Table 1: Optimization of reaction conditions.[a]



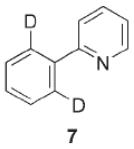
1a 2a 4a 5a

Entry	Catalyst	Peroxide	Yield of 4a + 5a [%] (4a/5a)[b]
1	—		
		3a	0
2	$Ru_3(CO)_{12}$	3a	0
3	$[\{RuCl_2(CO)_3\}_2]$	3a	0
4	$Ru(acac)_3$	3a	43 (1.3:1)
5	$[\{Ru(COD)Cl_2\}_2]$	3a	41 (2.4:1
6	$Ru(CO)H_2(PPh_3)_3$	3a	51 (1.5:1)
7	$[\{Ru(benzene)Cl_2\}_2]$	3a	40 (2.6:1)
8	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	58 (1.5:1)
9	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		20 (4.0:1)
10	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		33 (2.0:1)
11	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		40 (1.0:1)
12	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		0
13	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		0
14[c]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	50 (1.5:1)
15[d]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	35 (1.5:1)
16[e]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	80 (1:1)
17[e,f]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	0
18[e,g]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	3a	70 (7:1)

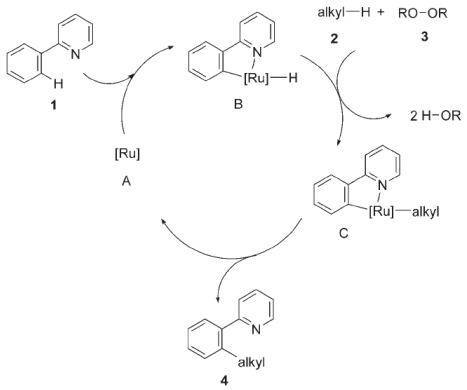
[a] **1a** (31 mg, 0.2 mmol), catalyst (10 mol%), cyclooctane (0.6 mL, 4.5 mmol), peroxide (2 equiv), 135 °C, 16 h in air unless otherwise noted. [b] Reaction was carried out at 120 °C. [c] Yields determined by using NMR methods in which 1,2-dichloroethane was the internal standard. [d] 5 mol% catalyst was used. [e] 4.0 equiv of peroxide used. [f] No cyclooctane was used. [g] Benzene was used instead of cyclooctane, and the yield was refers to the methylated product.



6



7



Scheme 2. Proposed mechanism for the ruthenium-catalyzed cycloalkylation of arenes mediated with peroxides.

Table 2: Cross-coupling of various arenes with cycloalkanes.[a]

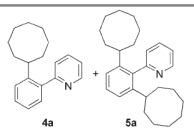
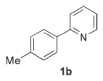
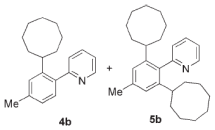
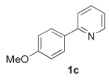
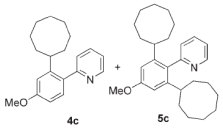
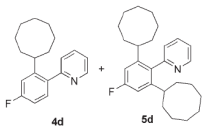
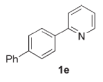
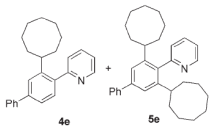
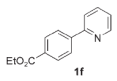
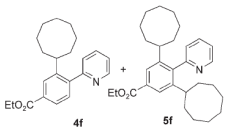
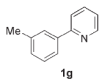
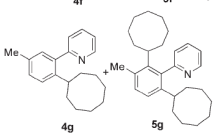
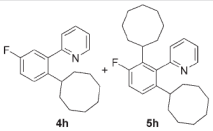
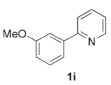
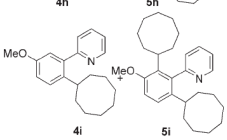
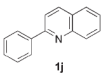
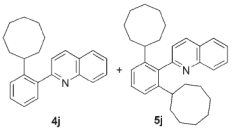
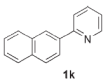
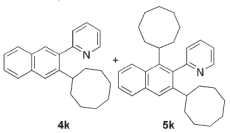
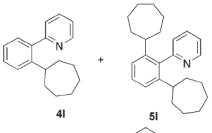
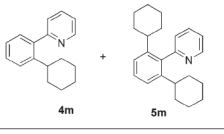
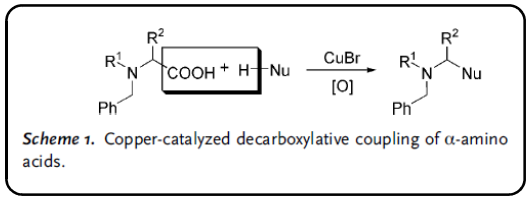
Entry	Arene	Alkane	Product	Yield [%][b]
1	 1a	 2a	 4a 5a	75 (4a/5a=1.1:1)
2[c]	1a	2a	4a + 5a	56 (4a/5a=1.5:1)
3	 1b	2a	 4b 5b	62 (5b, trace)
4	 1c	2a	 4c 5c	54 (5c, trace)
5[d]	 1d	2a	 4d 5d	71 (4d, trace)
6[c]	1d	2a	4d + 5d	60 (4d/5d=1:1)
7	 1e	2a	 4e 5e	63 (4e/5e=5:1)
8	 1f	2a	 4f 5f	63 (5f, trace)
9	 1g	2a	 4g 5g	53 (5g, trace)

Table 2: (Continued)

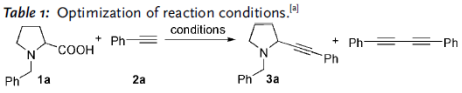
Entry	Arene	Alkane	Product	Yield [%][b]
10[c]	 1h	2a	 4h 5h	64 (5h, trace)
11	 1i	2a	 4i 5i	48 (5i, trace)
12	 1j	2a	 4j 5j	42 (5j, trace)
13	 1k	2a	 4k 5k	50 (5k, trace)
14	1a	 2b	 4l 5l	70 (4l/5l=1.1:1)
15	1a	 2c	 4m 5m	52 (4m/5m=1:1)

[a] **1** (0.2 mmol), *tert*-butyl peroxide (0.8 mmol), alkane (0.6 mL), 16 h in air unless otherwise noted. [b] Yields of isolated products. [c] 2 equiv *tert*-butyl peroxide was used. [d] The reaction was run for 6 h.



Scheme 1. Copper-catalyzed decarboxylative coupling of α-amino acids.

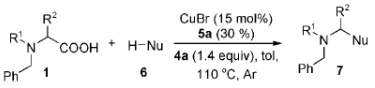
Table 1: Optimization of reaction conditions.[a]

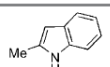
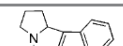
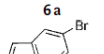
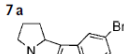
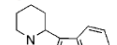
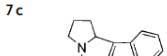
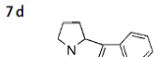
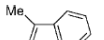
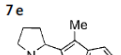
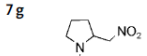
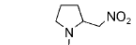


Entry	Catalyst	Oxidant	Ligand	NMR yield [%][b]	Dimer yield [%][c]
1	CuBr		–	42	8
2	CuBr		–	31	trace
3	CuBr		–	45	trace
4	CuBr		–	trace	6
5	CuBr	**4a** 	–	81	7
6	CuI	**4a**	–	65	11
7	CuOTf	**4a**	–	36	trace
8	CuCl	**4a**	–	54	trace
9	CuBr	**4a**	NEt_3	82	trace
10	CuBr	**4a**	**5a** 	90	trace
11	CuBr	**4a**		73	trace

[a] Reactions were carried out on a 0.3 mmol scale in toluene (1.5 mL) under argon at 110°C, overnight with **1a** (1.0 equiv), **2a** (1.5 equiv), oxidant (1.4 equiv), catalyst (0.15 equiv), and ligand (0.30 equiv). [b] Reported yields were based on **1a** and determined by NMR methods using an internal standard. [c] Yield of isolated product.

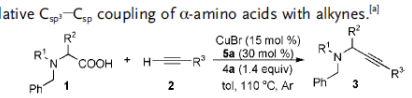
Table 3: Decarboxylative C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp} coupling of α-amino acids.[a]

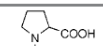
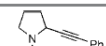
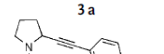
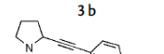
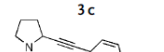
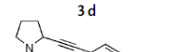
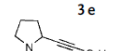
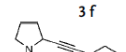
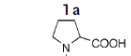
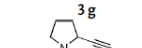
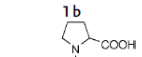
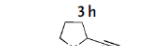
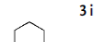
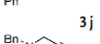


Entry	1	6	Product	Yield [%][b]
1	**1a**	 **6a**	 **7a**	87(74)
2	**1a**	 **6b**	 **7b**	87(74)
3	**1d**	 **6c**	 **7c**	78(63)
4	**1c**	**6c**	 **7d**	57(50)
5	**1b**	**6c**	 **7e**	82(69)
6	**1a**	 **6d**	 **7f**	0
7	**1a**	CH_3NO_2 **6e**	 **7g**	89(86)[c]
8	**1c**	**6e**	 **7h**	73(58)[c]
9	**1b**	**6e**	 **7i**	77(67)[c]

[a] α-Amino acid (1.0 equiv), nucleophile (1.5 equiv), **4a** (1.4 equiv), **5a** (30 mol%), and CuBr (15 mol%) in toluene (1.5 mL). [b] NMR yields are based on α-amino acid and determined by NMR methods using an internal standard; yield of isolated product is given in parentheses. [c] Used 3 equivalents of the nucleophile.

Table 2: Decarboxylative C_{sp^3}–C_{sp} coupling of α-amino acids with alkynes.[a]



Entry	1	R^3	Product	Yield [%][b]
1	 **1a**	Ph **2a**	 **3a**	90(80)
2	**1a**	4-$MeOC_6H_4$ **2b**	 **3b**	86(70)
3	**1a**	4-MeC_6H_4 **2c**	 **3c**	89(73)
4	**1a**	4-PhC_6H_4 **2d**	 **3d**	95(80)
5	**1a**	6-methoxynaphthalenyl **2e**	 **3e**	74(56)
6	**1a**	C_8H_{17} **2f**	 **3f**	83(65)
7	**1a**	1-cyclohexenyl **2g**	 **3g**	76(56)
8	 **1b**	**2a**	 **3h**	86(77)
9	 **1c**	**2a**	 **3i**	58(41)
10	 **1d**	**2a**	 **3j**	81(74)
11	 **1e**	**2a**	 **3k**	39(20)

[a] α-Amino acid (1.0 equiv), alkyne (1.5 equiv), **4a** (1.4 equiv), **5a** (30 mol%), and CuBr (15 mol%) in toluene (1.5 mL). [b] NMR yields are based on α-amino acid and determined by NMR methods using an internal standard; yield of isolated product is given in parentheses.

Scheme 2. Decarboxylative coupling reaction without CuBr.

Scheme 3. Proposed mechanism for the copper-catalyzed decarboxylative coupling between an α-amino acid and phenylacetylene.