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Stereospecific and Stereodivergent Construction of Quaternary Carbon Centers through Switchable Directed/Nondirected Allylic Substitution

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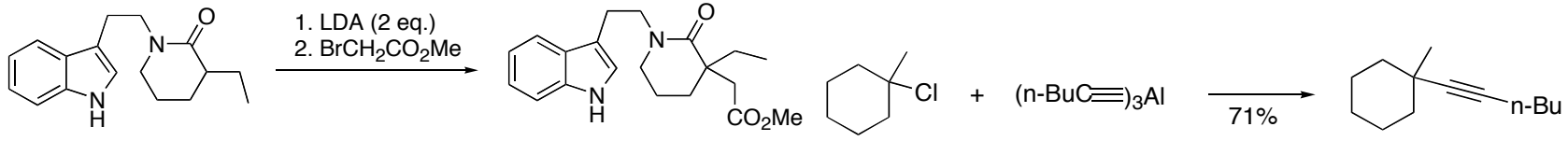
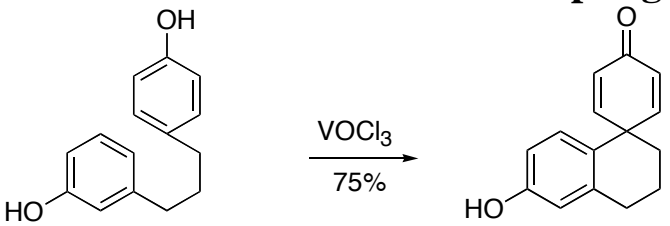
2004 Early View Communication

Quaternary Carbon Centers

1. Ionic constructions which may involve the participation of the tertiary carbon atom as a nucleophilic or as an electrophilic reaction partner



2. Oxidative and reductive coupling reactions



3. Rearrangement reactions

4. Cycloaddition reactions

Tetrahedron, **1980**, *36*, 419

Asymmetric Creation of Quaternary Carbon Centers

1. Enantioselective Creation (one chiral center was generated in product)

A. Enantiodifferentiating Reactions (0 to 1)
1. **Chemical Methods**
2. **Biological Methods**

B. Diastereodifferentiating Reactions (2 to 1)
1. **Use of Chiral Nucleofuges**
2. **Intramolecular Chiral transfer Reactions**
3. **Miscellaneous Reactions**

2. Diastereoselective Creation (two chiral centers were generated in product)

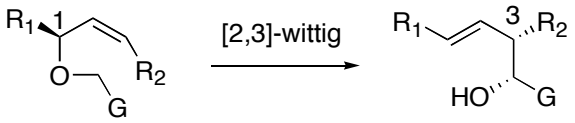
A. Enantiodifferentiating Reactions (0 to 2)

B. Diastereodifferentiating Reactions (1 to 2)
1. **Alkylation of Chiral Enamines**
2. **Alkylation of Chiral Enolates and relater Carbanions**
3. **D-A Cycloadditions**
4. **Micellaneous Reactions**

Chem. Rev., **1993**, *93*, 2037

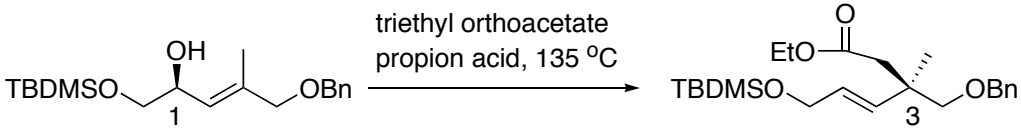
Intramolecular 1, 3-Chiral transfer Reactions

[2, 3]-Sigmatropic Rearrangement



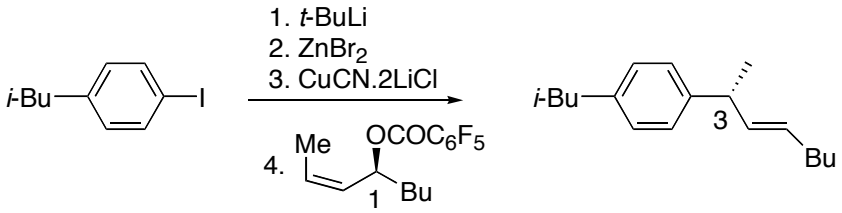
Chem. Rev., **1986**, *86*, 885

[3, 3]-Sigmatropic Rearrangement



Carb. Res., **2000**, *328*, 37

S_N2' Reaction



Org. Lett., **2003**, *5*, 2111

S_N2' Intramolecular 1, 3-Chiral transfer Reactions

Advantage:

1. **Allows the introduction of variable nucleophiles, such as alkyl, alkenyl and aryl groups into an existing carbon skeleton.**

2. **The reactions generally proceed by *anti* attack of the nucleophile with respect to the leaving group.**

Disadvantage:

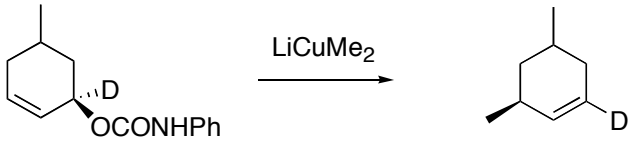
1. **Simultaneous control of the chemo-, regio- and stereo-chemistry is normally difficult.**

2. **The stereochemistry of the product was determined by the stereochemistry of the starting material.**

3. **Usually, excess of organometallic reagent is required to push the reaction to complete.**

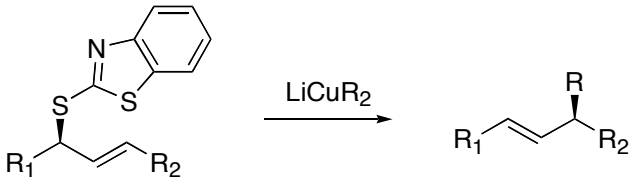
Reagent-directing leaving groups -*syn* attack

Carbamates as the leaving groups



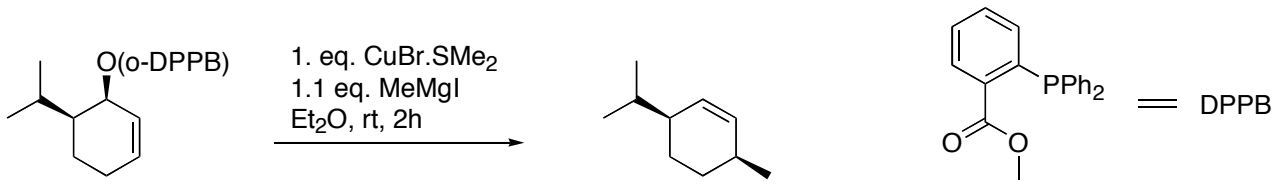
J. Org. Chem., **1983**, *48*, 715

Benzothiazole as the leaving group



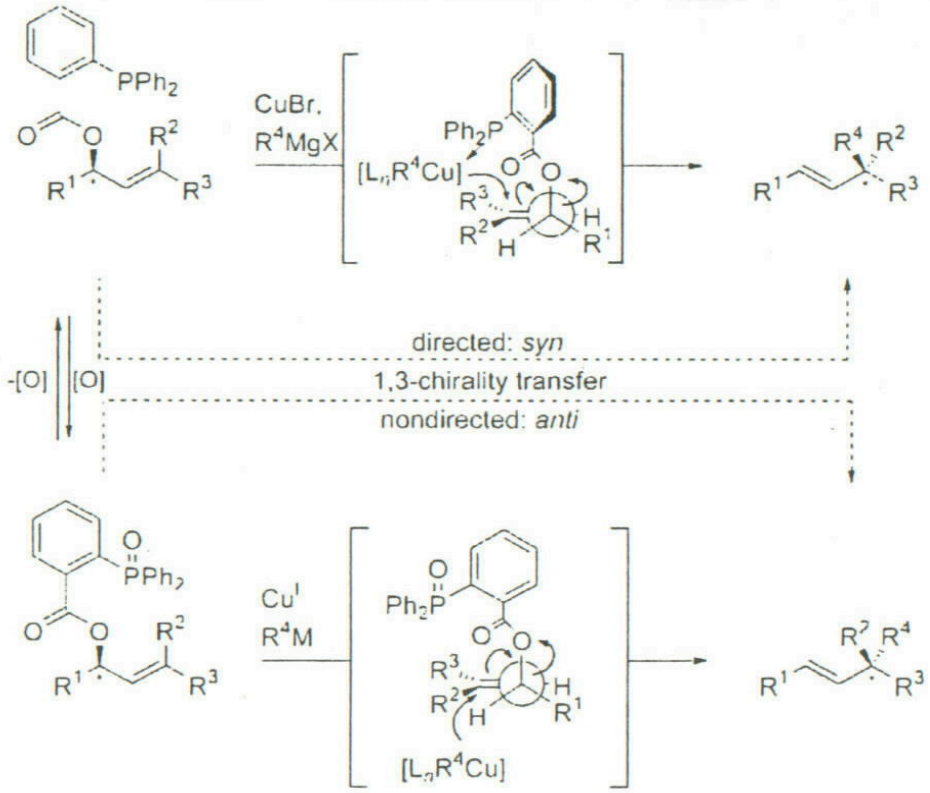
J. Org. Chem., **1990**, *55*, 2295

o-DPPB as the leaving group (DPPB = diphenylphosphanylbenzoate)



Adv. Synth. Catal., **2001**, *343*, 5

Switchable Directed/Nondirected Leaving Group

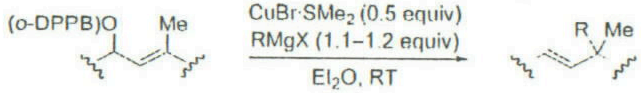


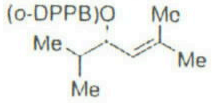
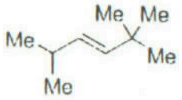
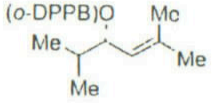
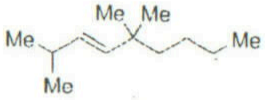
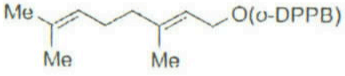
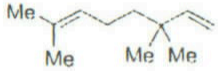
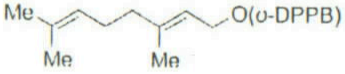
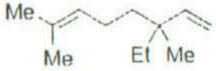
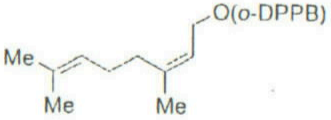
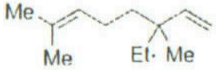
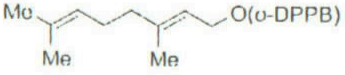
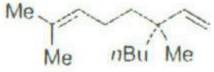
Scheme 1. Concept of stereodivergent allylic substitution with organocopper reagents for the stereospecific construction of quaternary carbon centers by employing a switchable directing/nondirecting leaving group.

ACEI, **2004**, Early View Communication

o-DPPB-directed Allylic Substitution

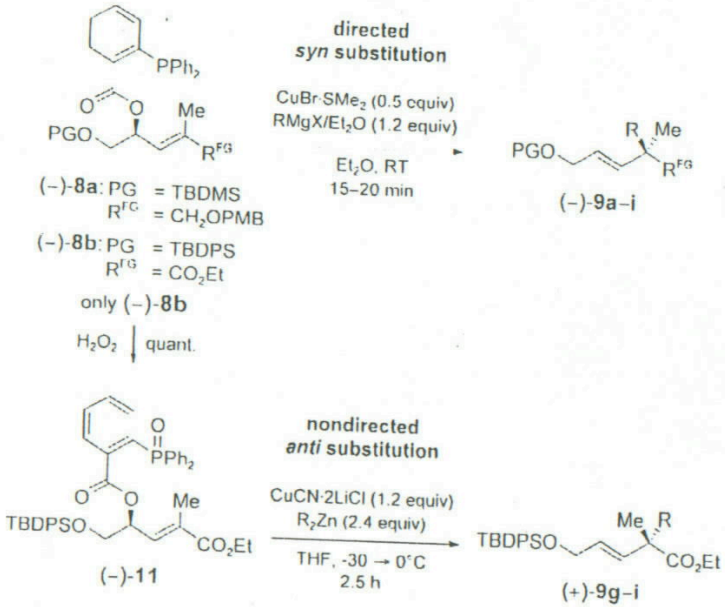
Table 1: Regioselective formation of quaternary carbon centers through *o*-DPPB-directed allylic substitution.[a]



Entry	*o*-DPPB ester[b]		RMgX (equiv)	Product		S_N2'/S_N2[c]	Yield [%][d]
1		**1**	MeMgI (1.1)		**2**	> 99:1	68[e]
2		**1**	*n*BuMgBr (1.1)		**3**	99:1	99
3		(*E*)-**4**	MeMgI (1.2)		**5**	95:5	91
4		(*E*)-**4**	EtMgBr (1.2)		**6**	> 98:2	80
5		(*Z*)-**4**	EtMgBr (1.2)		**6**	> 98:2	95
6		(*E*)-**4**	*n*BuMgBr (1.2)		**7**	> 99:1	87

[a] Reactions were performed in diethyl ether, c(*o*-DPPB ester) = 0.05 M. The Grignard reagent (0.51–1.23 M in diethyl ether) was added to the reaction mixture with a syringe pump over a period of 30 min. [b] Prepared from the corresponding allylic alcohol by an esterification protocol reported previously.[9] [c] Determined by GC (CPSil5CB, 30 m, 0.32 mm ID, Chrompack). [d] Yield of isolated product after distillation (entry 1) or chromatographic purification (entries 2–6). [e] The low yield is due to the volatility of the product.

Directed/Nondirected Allylic Substitution



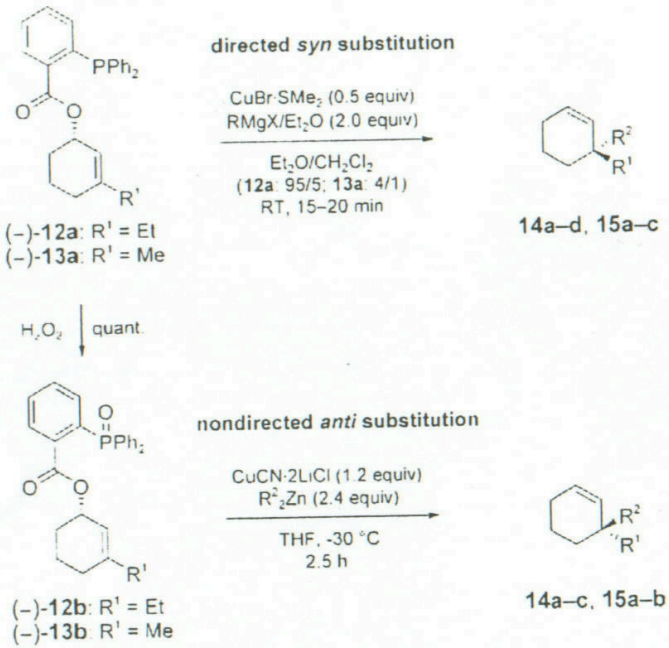
Scheme 2. Stereospecific and stereodivergent construction of quaternary carbon centers through the switchable directed/nondirected allylic substitution of the acyclic substrates (–)-**8a/b** and (–)-**11** (see Table 2). PG = protecting group, PMB = *p*-methoxybenzyl, TBDMS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

Table 2: Stereospecific and stereodivergent formation of quaternary carbon centers: acyclic substrates.[a]

Entry	Substrate[b] (*ee* [%])	R^2	S_N2'/S_N2[c]	E/Z[c]	Product (*ee* [%])[c]	CT[d] [%]	Yield[e] [%]
1	**8a** (94)	Me	>95:5	>95:5	**9a**	–	72
2	**8a** (94)	Et	>99:1	>99:1	(–)-**9b** (94)	100	86
3	**8a** (93)	*n*Bu	>99:1	>99:1	(–)-**9c** (93)	100	99
4	**8a** (93)	*i*Pr	>99:1	>99:1	(–)-**9d** (93)	100	89
5[f]	**8a** (93)	Bn	>99:1	>99:1	(–)-**9e** (85)	91	53
6	**8a** (92)	*t*Bu	14:86[g]	80:20[g]	**9f** (n.d.[i])	n.d.[h]	90
7	**8b** (>99)	Et	>99:1	>99:1	(–)-**9g** (98)	98	84
8	**8b** (>99)	*n*Bu	>99:1	>99:1	(–)-**9h** (97)	98	87
9	**8b** (>99)	*i*Pr	>99:1	>99:1	(–)-**9i** (97)	98	84
10	**11** (>99)	Et	>99:1	>99:1	(+)-**9g** (99)	100	85
11	**11** (>99)	*n*Bu	>98:2	>98:2	(+)-**9h** (99)	100	87
12[f]	**11** (>99)	*i*Pr	97:3[g]	>95:5	(+)-**9i** (>99)	100	94

[a] All reactions were performed in diethyl ether, c(*o*-DPPB ester) = 0.05 M. The Grignard reagent (0.76–1.23 M in diethyl ether) was added to the reaction mixture with a syringe pump over a period of 15–20 min. [b] Prepared from the corresponding allylic alcohol[12] by an esterification protocol reported previously.[9] The enantiomeric excess was determined by HPLC analysis of the corresponding allylic alcohol (Chiralpak AD (**8a**), Chiralcel OD-H (**8b**)). [c] Determined by ^{1}H NMR spectroscopy (entry 1) or HPLC analysis (entries 2, 3, 5, 7, 9: Chiralcel OD-H; entry 4: Chiralpak AD after removal of the TBDMS group; entries 9, 12: Chiralcel OD-H after removal of the TBDPS group). [d] The chirality transfer (CT) was calculated as CT = (*ee*(**9**)/*ee*(**8** or **11**)) × 100. [e] Yield of isolated product after chromatographic purification. [f] c(**8a**) = 0.01 M in diethyl ether; the Grignard reagent (0.07 M in diethyl ether) was added over a period of 90 min. [g] Product ratios were determined by ^{1}H NMR spectroscopy. [h] n.d. = not determined. [i] With 1-methyl-2-pyrrolidinone (NMP) as a cosolvent (one third of the total solvent volume).

Application of Switchable Directed/Nondirected Substitution in Six-membered-ring System



Scheme 3. Stereospecific and stereodivergent construction of quaternary carbon centers through the switchable directed/nondirected allylic substitution of the cyclic substrates (–)-12a/b and (–)-13a/b (see Table 3).

Table 3: Stereospecific and stereodivergent formation of quaternary carbon centers: cyclic substrates.

Entry	Substrate[a] (*ee* [%])	R	S_N2'/S_N2[b]	Product (*ee* [%])[b]	CT[c] [%]	Yield[d] [%]
1[e]	**12a** (97)	Me	99:1	(+)-**14a** (96)	99	>95
2[e]	**12a** (97)	*n*Bu	>99:1	(+)-**14b** (96)	99	>95
3[e]	**12a** (97)	*i*Pr	98:2	(–)-**14c** (96)	99	>95
4[e]	**12a** (97)	Ph	40:60	(+)-**14d** (92)	95	>95
5[f]	**13a** (94)	Et	96:4	(–)-**14a** (91)	97	>95
6[f]	**13a** (94)	*n*Bu	98:2	(+)-**15a** (94)	100	>95
7[f]	**13a** (94)	*i*Pr	96:4	(–)-**15b** (91)	97	>95
8[f]	**13a** (94)	Ph	41:59	(+)-**15c** (82)	87	>95
9[g]	**12b** (97)	Me	99:1	(–)-**14a** (93)	96	>95
10[g]	**12b** (97)	*n*Bu	>99:1	(–)-**14b** (96)	99	>95
11[g]	**12b** (97)	*i*Pr	97:3	(+)-**14c** (94)	97	>95
12[g]	**13b** (94)	Et	>99:1	(+)-**14a** (93)	99	>95
13[g]	**13b** (94)	*n*Bu	99:1	(–)-**15a** (94)	100	>95
14[g]	**13b** (94)	*i*Pr	99:1	(+)-**15b** (93)	99	>95

[a] Prepared from the corresponding allylic alcohol following an esterification protocol reported previously.[9] The enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H (**12a**), Chiralcel OD-H (**13a**)). [b] Determined by ^{1}H NMR spectroscopy and GC analysis (Supelco Beta Dex 110 (**14a**,**14d**,**15c**), C.E.I. G-TA (**14b**,**14c**,**15a**,**15b**)). [c] The chirality transfer (CT) was calculated as CT = (*ee*(**14**)/*ee*(**12**)) × 100. [d] Yield was determined by GC. [e] The Cu-complexed *o*-DPPB esters were added in diethyl ether/dichloromethane (95:5, *c* = 0.01 M) to the Grignard reagent (0.05 M in diethyl ether) by using a syringe pump (6 mL h^{-1}). [f] As for [e], but diethyl ether/dichloromethane (4:1, *c* = 0.01 M). [g] The oxidized *o*-DPPB esters (*c* = 0.07 M in THF) were added to the zinc–copper reagents (*c* = 1.00 M in THF) at a rate of 12 mL h^{-1}.

Conclusion

1. **The o-DPPB/o-DPPB oxide system can be used as a switchable directing/nondirecting leaving group in a copper-mediated allylic substitution reactions.**

2. **Both enantiomers of the substitution product are readily available from one enantiomer of the substrate.**

3. **The chemo-, regio- and stereoselectivity are quite good.**

4. **Large excess of organometallic reagents is NOT necessary.**

5. **The switchable leaving groups are reusable.**