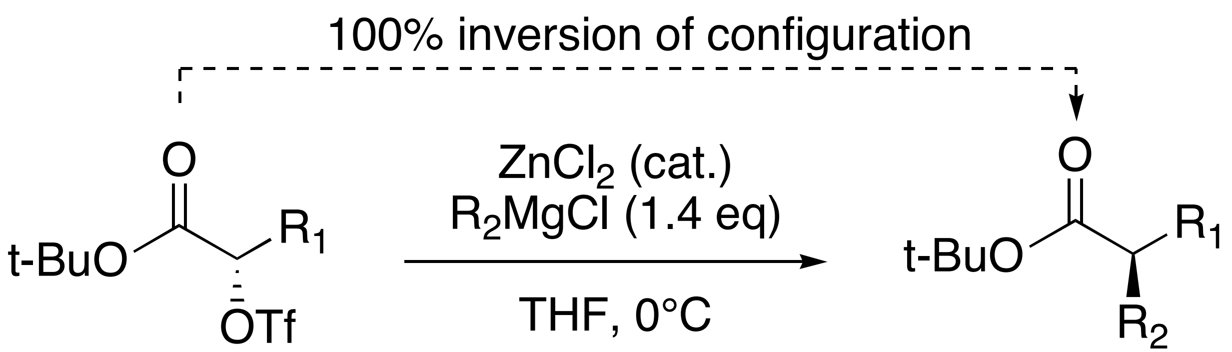
Zinc-Catalyzed Enantiospecific sp^3-sp^3 Cross-Coupling of α-Hydroxy Ester Triflates with Grignard Reagents

Christopher Studte and Bernhard Breit

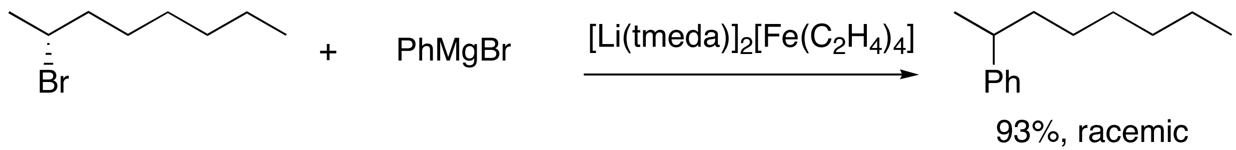
Angew. Chem. Int. Ed. **2008**, Early View

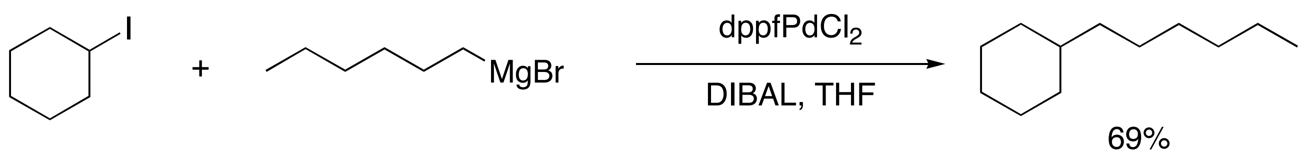


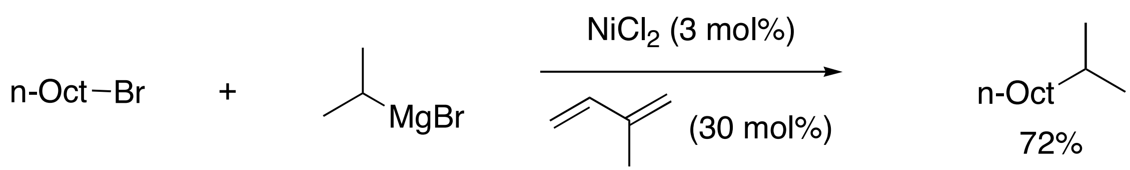
R_1, R_2 = Me, n-, s-, alkyl^{FG} 28 examples, 72 to > 99% yield

Nate Ware
Current Literature
6/28/08

Examples of Cross-Coupling Reactions with Secondary Electrophiles

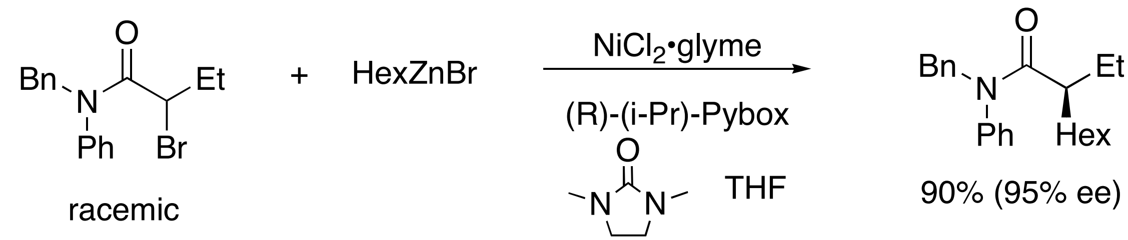


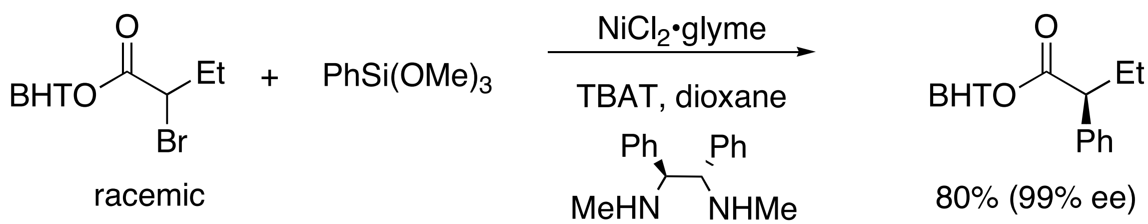


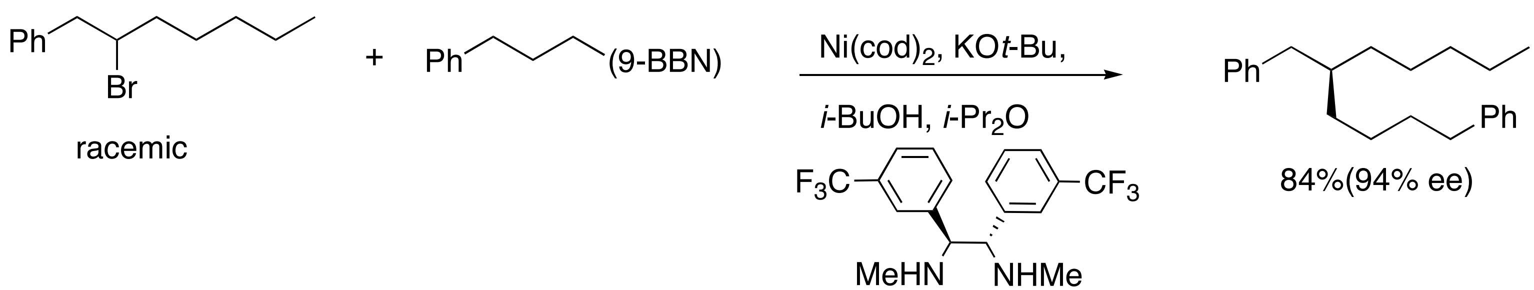


Martin and Fürstner. *Angew. Chem. Int. Ed*. **2004**, *43*, 3955
Castle and Widdowson. *Tetrahedron Lett*. **1986**, *27*, 6013
Terao et al. *J. Am. Chem. Soc*. **2002**, *124*, 4222

Racemic Bromides as a Prochiral Alkyl-Alkyl Cross-Coupling Partners







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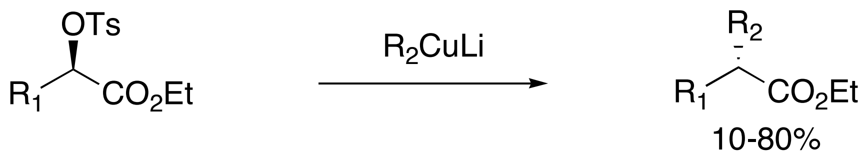
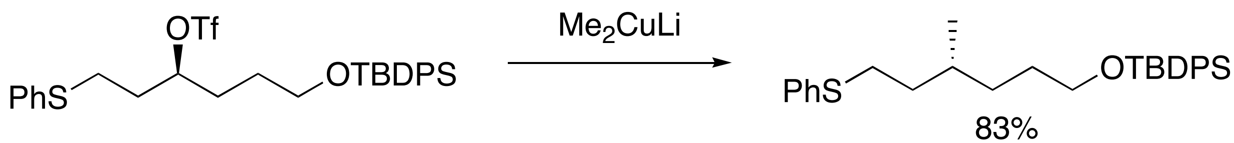
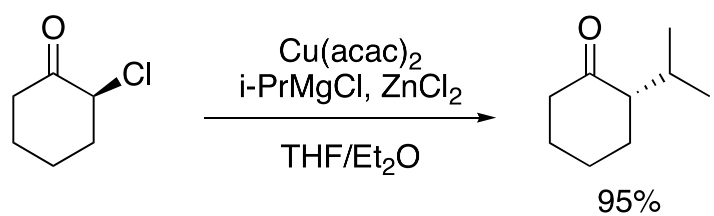
Stereoselective sp^3-sp^3 Cross-Couplings Using Copper Reagents







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Hanessian et al. *J. Org. Chem*. **1989**, *54*, 5831
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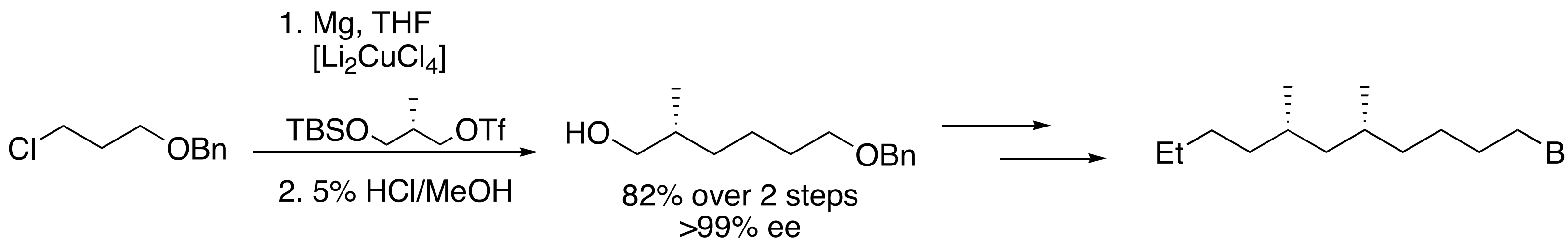
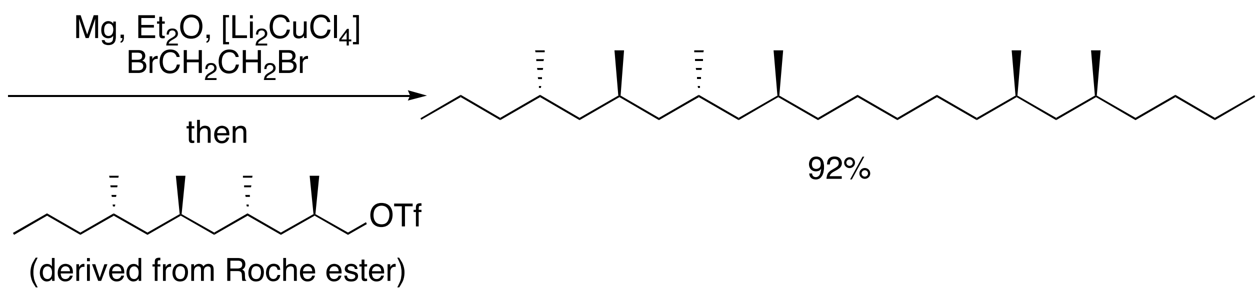
Previous Work Using sp^3-sp^3 Cross-Couplings in the Breit Group

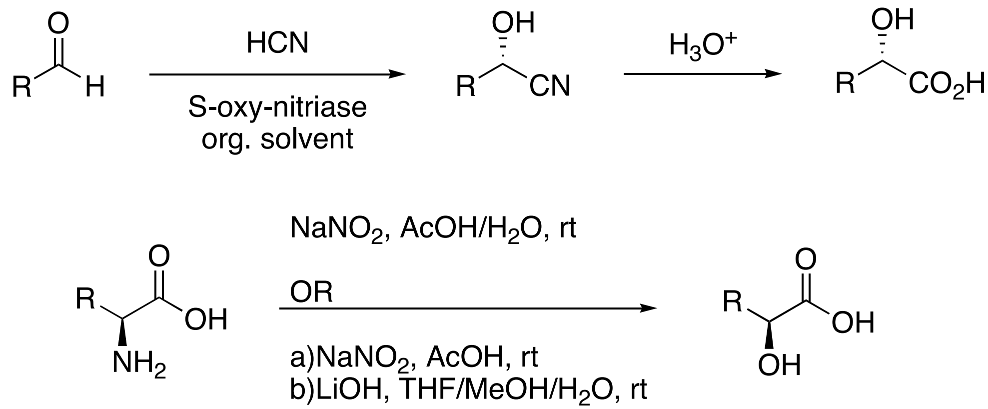




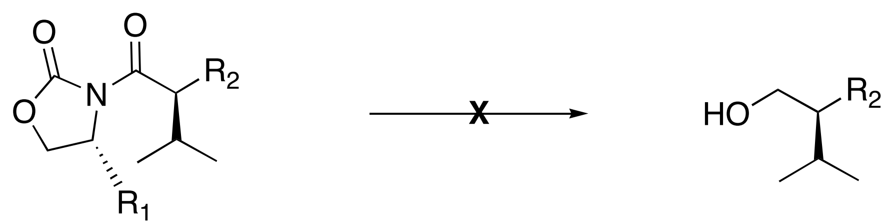
Heber and Breit. *Angew. Chem. Int. Ed*. **2005**, *44*, 5267
Heber and Breit. *Eur. J. Org. Chem.* **2007**, 3512

Advantages of a Direct Alkyl Coupling of α-Substituted Esters.

Easily obtained starting materials from the chiral pool, enzymatic construction of chiral cyanohydrins, or from α-amino acids.

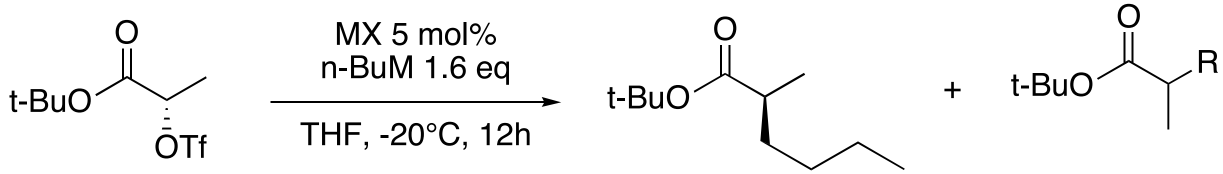


Can avoid chiral auxiliaries on sterically congested molecules.



Effengerger *Angew. Chem. Int. Ed.* **1994**, *33*, 1555 (Rev.)
Deechongkit et al. *Org. Lett.* **2004**, *6*, 497

Title Paper
Determination of Transition Metal Catalyst



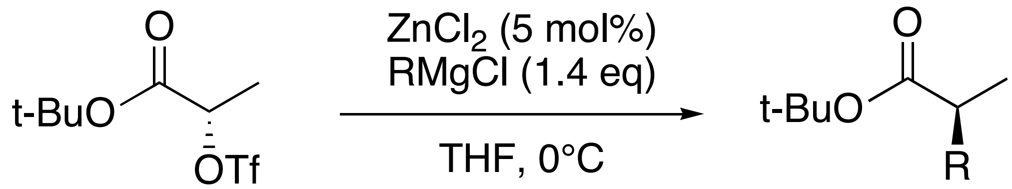
(-)-1a

(+)-2a

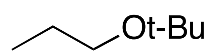
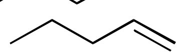
3: R=Cl
4: R=homodimer
5: R=H

Entry	Cat. MX_n	n-Bu-M	**2a** [%]	Conv. [%]
1	--	*n*-BuMgCl	46	62
2	[Fe(acac)$_3$]	*n*-BuMgCl	0	>99
3	Li_2CuCl_4	*n*-BuMgCl	56	>99
4	$ZnCl_2$	*n*-BuMgCl	>99	>99
5	$ZnCl_2$	*n*-BuMgBr	11	>99
6	$ZnCl_2$	*n*-BuLi	0	>99

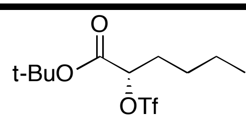
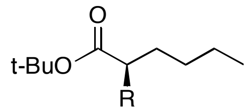
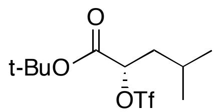
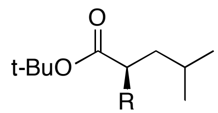
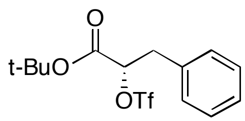
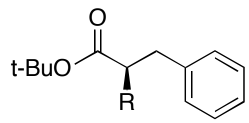
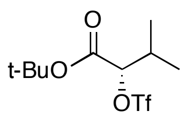
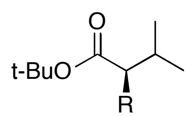
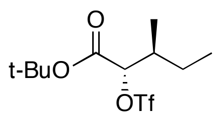
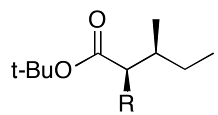
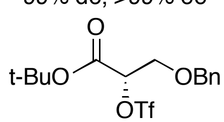
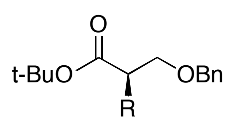
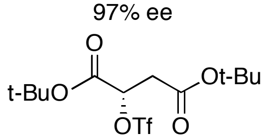
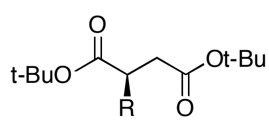
Reaction Scope for the Grignard Reagent



(-)1a >99%ee (+)-2a-k

Entry	R	Product	Yield [%]	*ee* [%]	CT [%]
1	Et	**(+)-2b**	>99	>99	100
2	*i*-Pr	**(+)-2c**	98	>99	100
3	n-Bu	**(+)-2a**	>99	>99	100
4	i-Bu	**(+)-2d**	>99	>99	100
5	s-Bu	**(+)-2e**	96	>99	100
6	Cy	**(+)-2f**	90	>99	100
7	Oct	**(+)-2g**	>99	>99	100
8	lauryl	**(+)-2h**	>99	>99	100
9	Bn	**(+)-2i**	>99	>99	100
10		**(+)-2j**	94	>99	100
11		**(+)-2k**	>99	>99	100

Reaction Scope for the Side Chain

Entry	R	Product	R	$ZnCl_2$ [mol%]	Yield [%]	*ee* [%]
1	 >99% ee		Me	20	92	99
2			Et	5	>99	99
3			i-Pr	15	88	99
4	 >99% ee		Me	20	81	>99
5			Et	10	>99	>99
6			i-Pr	15	79	>99
7	 98% ee		Me	20	72	98
8			Et	5	>99	98
9			i-Pr	20	84	98
10	 >99% ee		Me	50	76	>99
11			Et	15	>99	>99
12			n-Bu	20	>99	>99
13	 99% de, >99% ee		Me	50	73	99
14			Et	20	>99	99
15			n-Bu	20	>99	99
16	 97% ee		Et	20	95	97
17	 >99% ee		Me	20	74	>99

Conclusions

- The first zinc-catalyzed enantiospecific coupling reaction of sp^3 hybridized carbons was developed and was used to produce α-substituted esters from readily available starting materials.
- Provides an alternative approach to this motif from enolate alkylations.