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Uniting Anion Relay Chemistry with Pd-Mediated Cross Coupling: Design, Synthesis and Evaluation of Bifunctional Aryl and Vinyl Silane Linchpins

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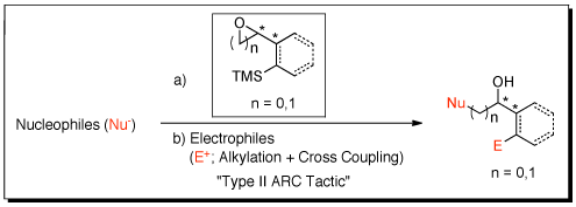
Abstract



Union of Type II Anion Relay Chemistry (ARC) with Pd-induced Cross Coupling Reactions (CCR) has been achieved, in conjunction with the design, synthesis, and evaluation of a new class of bifunctional linchpins, comprising a series of vinyl silanes bearing β- or γ-electrophilic sites. The synthetic tactic permits both alkylation and Pd-mediated CCR of the anions derived via 1,4-silyl C (sp^2)→O Brook Rearrangements.

Type I and II Anion Relay Chemistry (ARC),[1] exploiting Brook Rearrangements (Scheme **1A** and **1B**),[2] comprises a powerful linchpin tactic for the rapid assembly of high levels of molecular complexity, as demanded by natural product total synthesis. Extension of the Type II ARC process (Scheme **1B**) to include transition metal promoted Cross-Coupling Reactions (CCR), as the culminating event in the Type II ARC process (cf. **8**→**9**) would, in general, greatly extend the scope of this evolving synthetic tactic. Recently, we recorded a single example employing *ortho*-TMS benzaldehyde **10** as linchpin that demonstrated the feasibility of uniting Anion Relay Chemistry with Pd-mediated cross coupling (Scheme 2).[3] The reaction sequence involved treatment of **10** with *n*-BuLi followed in turn by addition of CuI and HMPA to induce 1,4-silyl C(sp^2)→O migration, vinyl bromide with a catalytic amount of $Pd(PPh_3)_4$ for the CCR, and TBAF to remove the TMS group; tricomponent adduct **10a** was produced in 56% yield.

Convinced that this “one-flask” multicomponent protocol would hold considerable potential, in general, we initiated a program to unite Anion Relay Chemistry with the cross coupling tactic. We quickly recognized, as reported by Takeda *et al*.[4] for *ortho*-TMS benzyl alcohol, that the use of CuI, and in our case a mixture of HMPA and THF (1:1), is required to trigger the 1,4-Brook rearrangement. Towards this end, addition of *n*-BuLi to **10**, followed by CuI/HMPA:THF induced silyl migration. Subsequent addition of diverse vinyl and aryl halides in

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Supporting Information Available: Procedures and characterization data are available free of charge via the Internet: http://pubs.acs.org.

the presence of 3 mol % $Pd(PPh_3)_4$ in THF at room temperature then, led to a series of cross coupled adducts (**10a**-**10h**) with yields ranging from 50-67% (Table 1).

Having established the initial scope of the combined ARC-II/Pd-mediated CCR protocol, we turned to the design, synthesis and evaluation of a new class of bifunctional vinyl silanes, with electrophilic sites β or γ to the silane (Figure 1), first to explore their utility as linchpins for the Type II ARC tactic and then as linchpins in the combined ARC-II/Pd-mediated CCR process.

Linchpin **11** was readily available via oxidation of known alcohol **17**,[5] while **12** was prepared from epoxide **18**[6] and commercial vinyl bromide **19** (Scheme 3).

To explore the ARC tactic with **11**, we selected conditions that proved effective with **10**.[3] As illustrated in Table 2, addition of *n*-BuLi in Et_2O, followed by CuI (1.2 equiv) in a mixture of HMPA/THF (1:1), and then a variety of carbon- and heteroatom-based electrophiles furnished adducts **21a-21d** in 63-68% yield. Under these conditions, the 1,4 silyl migration proceeded rapidly (ca. 30 min). Equally important, palladium-mediated cross coupling reactions, initiated via the ARC Type II process, proved feasible. For example, addition of 3 mol % $Pd(PPh_3)_4$ and a series of vinyl and aryl halides after the HMPA/THF induced Brook rearrangement furnished cross coupled adducts **21e-22h** in 52-61% yield. Other common nucleophiles proved effective as initiators of both the Type II ARC and the combined ARC-II/Pd-mediated CCR tactics (Table 3). Use of TBAF to remove the TMS group proved critical to avoid partial allylic rearrangements of **22a-22f**; use of 1 N HCl led to facile allylic rearrangement (cf. **22h**-**22j**). Neither allylic rearrangement nor cross-coupling was observed upon use of anion derived from dithiane, the latter due to catalyst poisoning by the dithiane.[7]

Encouraged by the viability of the Type II ARC process employing **11**, we turned next to **12** as the bifunctional linchpin (Table 4). Initially, silyl migration proved problematic, furnishing only trace amounts of the desired product when employing the conditions which proved effective at triggering silyl migration with **11**. However, when two equivalents of both *n*-BuLi as the nucleophile and CuI were employed in a mixture of HMPA and THF (1:1), complete 1,4-silyl $C(sp^2)\rightarrow O$ migration occurred albeit more slowly over the course of 2 h. Addition of a series of electrophiles (2.0 equiv) furnished alkylation adducts **23a-23d** (Table 4, Entries 1-4) in ca. 50% yield, while modest yields of cross-coupling products **23e**-**23f** were obtained upon addition of 3 mol % $Pd(PPh_3)_4$ followed by aryl iodides (Entries 5-6).

The variable time course between **11** and **12** for 1,4-silyl group migration is understandable in terms of the mechanism of the Brook rearrangement.[8] In the case of linchpin **12**, the 1,4-silyl $C(sp^2)\rightarrow O$ migration is slow, due to a combination of the distance between the silicon and oxygen atoms and the multiple bond rotations required to arrive at the cyclic transition state.[9]

From the perspective of complex molecule synthesis, a drawback of employing α-unsubstituted linchpin aldehydes **11** and **12** entails the lack of stereochemical control upon initial nucleophilic addition and the lack of the ubiquitous methyl substituents found in polyketides. We therefore turned to α-substituted linchpins (+)-**13** and (−)-**14**.[10] We reasoned that addition of alkyllithiums to (+)-**13** and (−)-**14** would produce, with good diastereoselectivity, the corresponding *syn* alkoxides. Confirmation of this scenario would further increase the utility of both the Type II ARC and ARC-II/Pd-induced CCR tactics, not only for natural product total synthesis, but also polyketide diversity synthesis.[11]

Pleasingly, addition of *n*-BuLi to either (+)-**13** or (−)-**14** (Table 5), followed in turn by silyl migration induced by CuI in a mixture of HMPA and THF (1:1) and reaction with a series of electrophiles furnished multicomponent adducts **24a-25h** in yields ranging from 56 to 75% (Table 5).[12] Effective cross coupling unions also occurred after 1,4-Brook rearrangement, upon

addition of 3 mol % $Pd(PPh_3)_4$, followed by vinyl or aryl halides. Importantly, no epimerization of the α-methyl substituent was observed during this process.

As with linchpin **11**, other nucleophiles derived from furan, phenyl bromide and 2-methyl-1,3-dithiane prove to be effective at initiating the Type II ARC tactic to furnish, in a single flask, both three-component alkylation and cross-coupled adducts **26a-27e** (Table 6).

We next explored the possibility of extending the Type II ARC and ARC-II/Pd-induced CCR tactics to epoxide-based linchpins possessing an electrophilic site γ to the vinyl silane. This design led to linchpins (−)-**15** and (+)-**16**, constructed as illustrated in Scheme 4.[13,14]

With the four-carbon bifunctional linchpins in hand, we employed lithium dibutylcuprate **31**, known both to add to epoxides[15] and to initiate 1,4-silyl $C(sp^3)\rightarrow O$ migration in Anion Relay Chemistry.[1b] Capture of allyl bromide after Brook rearrangement led respectively to adducts (+)-**32** and (+)-**34** (Scheme 5). Cross coupling reactions also proceeded upon addition of 3 mol % $Pd(PPh_3)_4$, followed by reaction with phenyl iodide to furnish (+)-**33** and (+)-**35**, respectively.

In summary, the union of Type II Anion Relay Chemistry with Pd-mediated Cross Coupling has been achieved, thereby greatly expanding the scope of this multicomponent “one-flask” linchpin protocol. Equally important, a new class of three and four carbon, bifunctional linchpins comprising aryl and vinyl silanes bearing β- or γ-electrophilic sites, have been designed, synthesized and demonstrated to be competent in both Type II ARC and combined ARC-II/Pd-induced CCR processes. Studies to improve the efficiency of this tactic continue in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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3. Smith AB III, Kim W-S, Wuest WM. Angew. Chem., Int. Ed 2008;47:7082.
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9. The results on silyl migration are in accord with Takeda and coworkers. Tsubouchi A, Itoh M, Onishi K, Takeda T. Synthesis 2004;9:1504.
10. Sato and coworkers demonstrated (+)-**13** and (−)-**14** underwent Grignard reactions with high *syn* diastereoselectivity, the result of a Cram product-like transition state.[10b,10e] (a) Sato F, Kusakabe M, Kobayashi Y. J. Chem. Soc., Chem. Commun 1984:1130. (b) Sato F, Takeda Y, Uchiyama H, Kobayashi Y. J. Chem. Soc., Chem. Commun 1984:1132. (c) Kobayashi Y, Kitano Y, Sato F. J. Chem. Soc., Chem. Commun 1984:1329. (d) Sato F, Kusakabe M, Kato Y. J. Chem. Soc., Chem.

Commun 1984:1331. (e) Samaddar AK, Chiba T, Kobayashi Y, Sato F. J. Chem. Soc., Chem. Commun 1985:329.

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12. Absolute configuration was confirmed by Mosher ester analysis.
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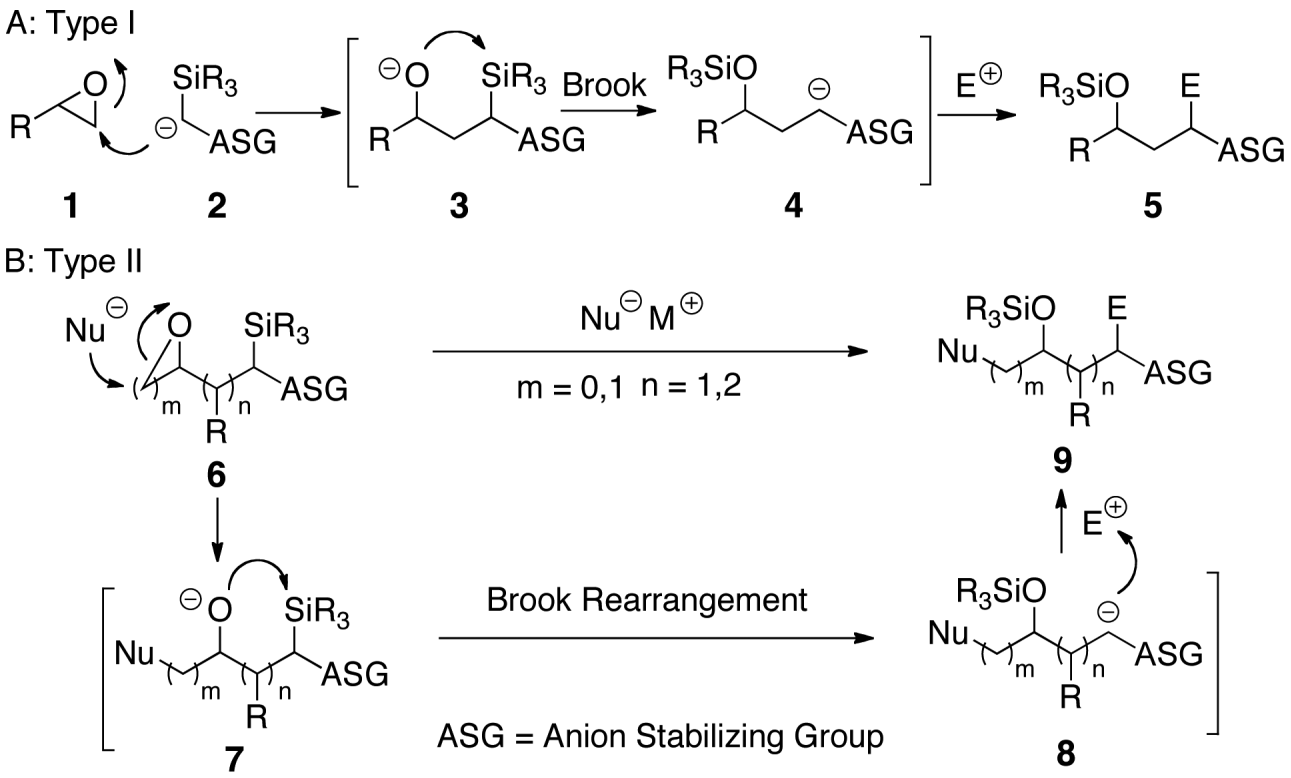
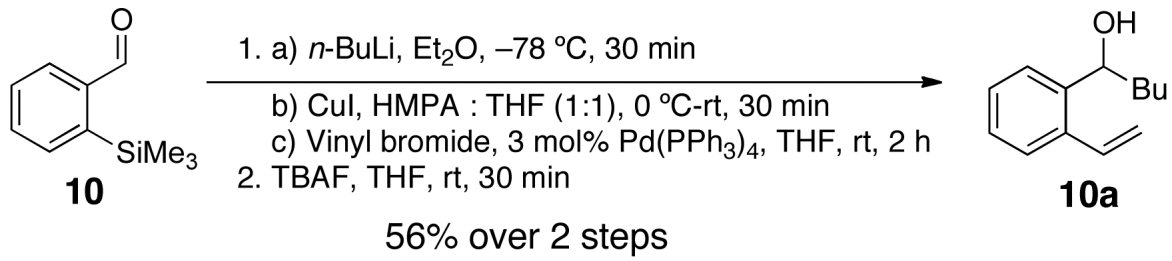


Scheme 1.
Type I and II Anion Relay Chemistry (ARC)



Scheme 2.
Type II Anion Relay Chemistry (ARC) and Cross-Coupling Reactions (CCR).

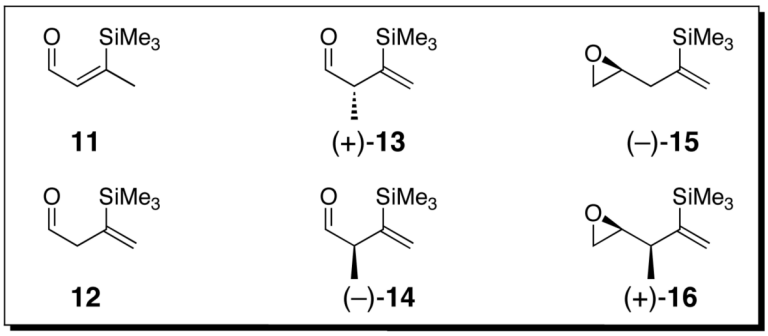
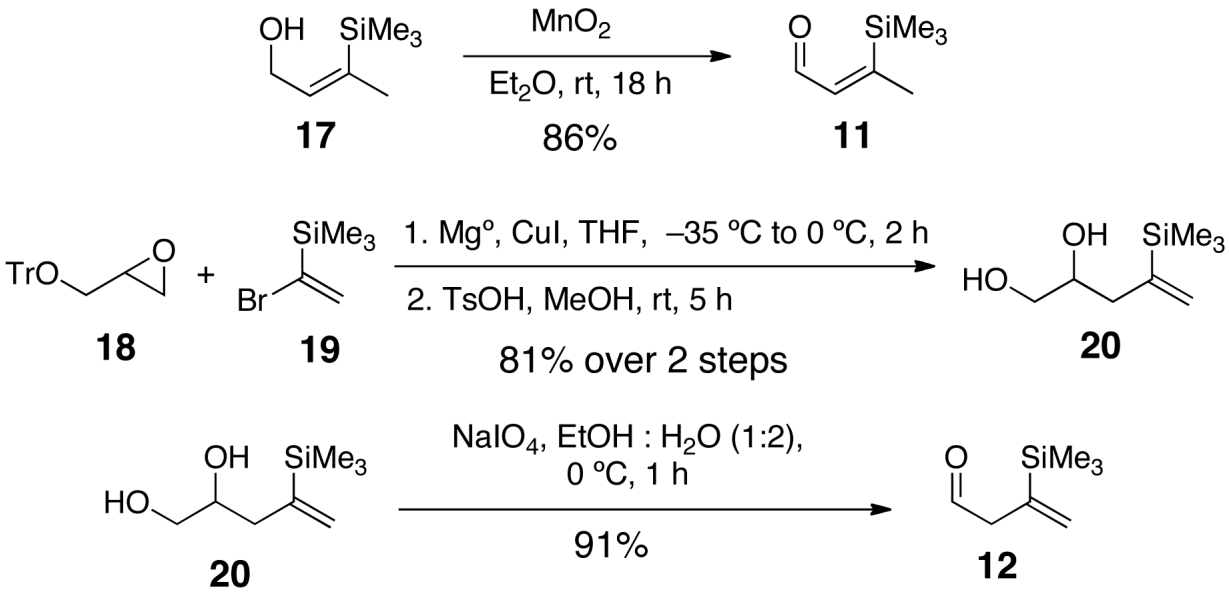
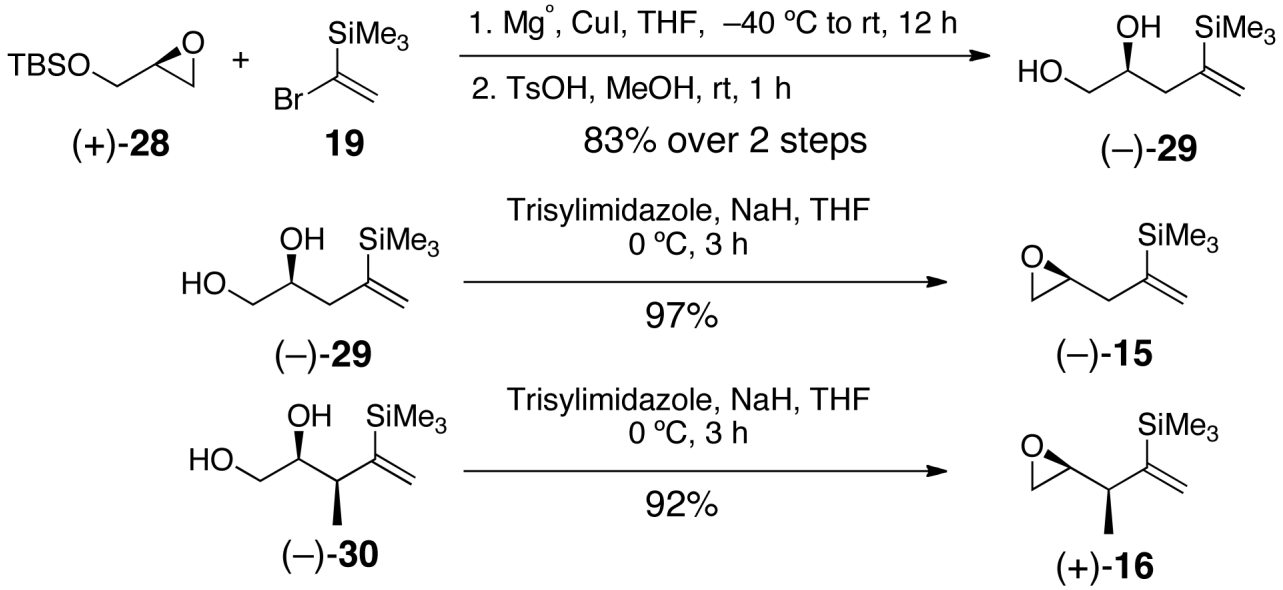


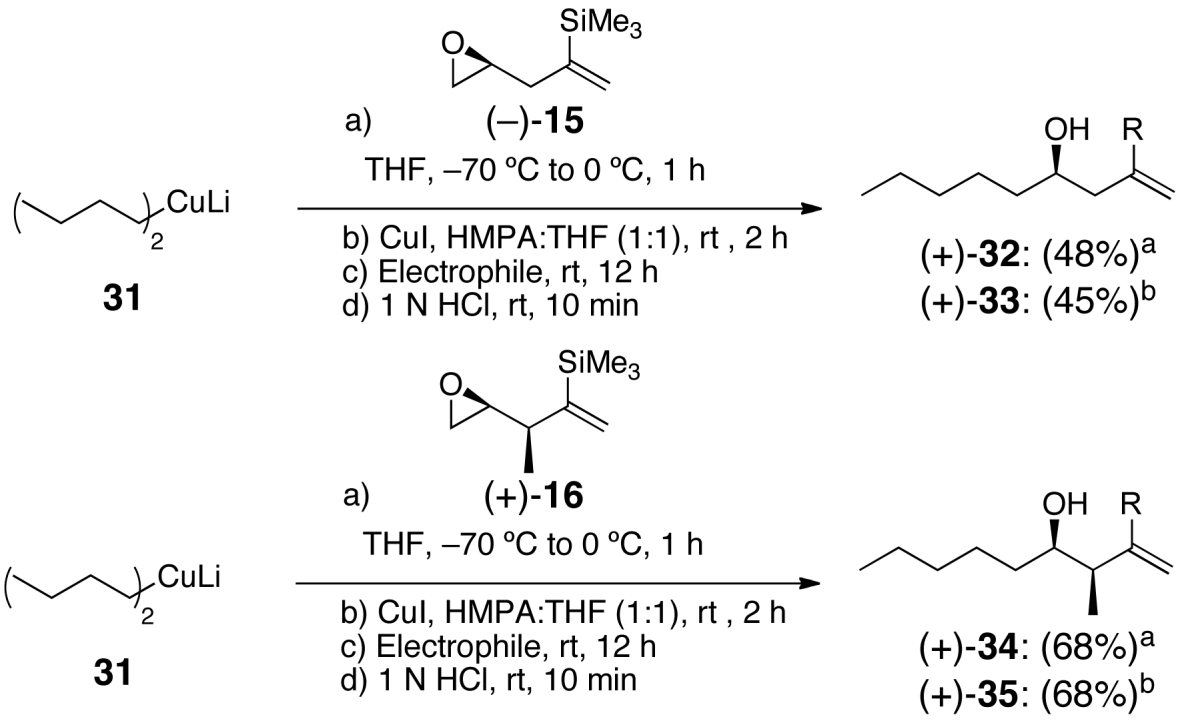
Figure 1.
Vinyl Silane Bifunctional Linchpins



Scheme 3.
Preparation of Linchpins **11** and **12**



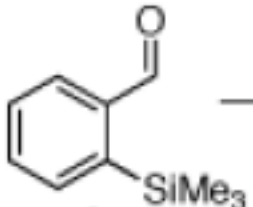
Scheme 4.
Preparation of Linchpins (−)-**15** and (+)-**16**



Scheme 5.
Three-Component Coupling of Linchpins (−)-**15** or (+)-**16** with Various Electrophiles

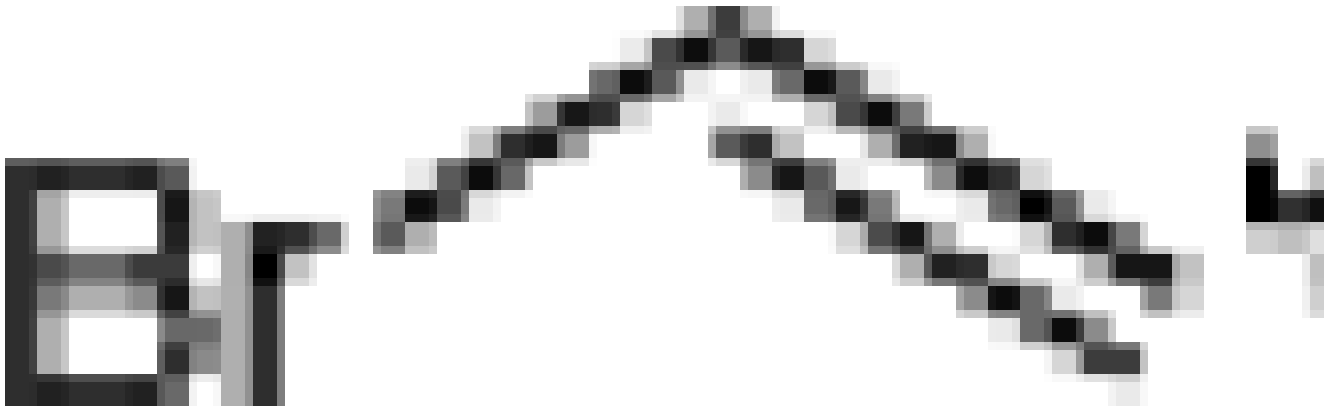
Table 1

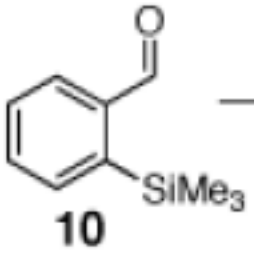
Pd-Mediated Cross-Coupling Reactions via Type II ARC



10

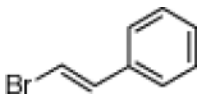
a) *n*-BuLi, Et_2O, - 78 °C, 3
b) CuI, HMPA:THF (1:1), r
c) Electrophile, 3 mol % P
THF, rt, 6 h
d) 1 N HCl, rt, 10 min

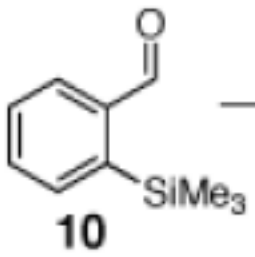
entry	electrophile
1	



10

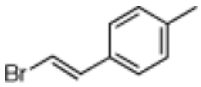
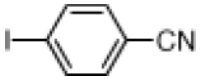
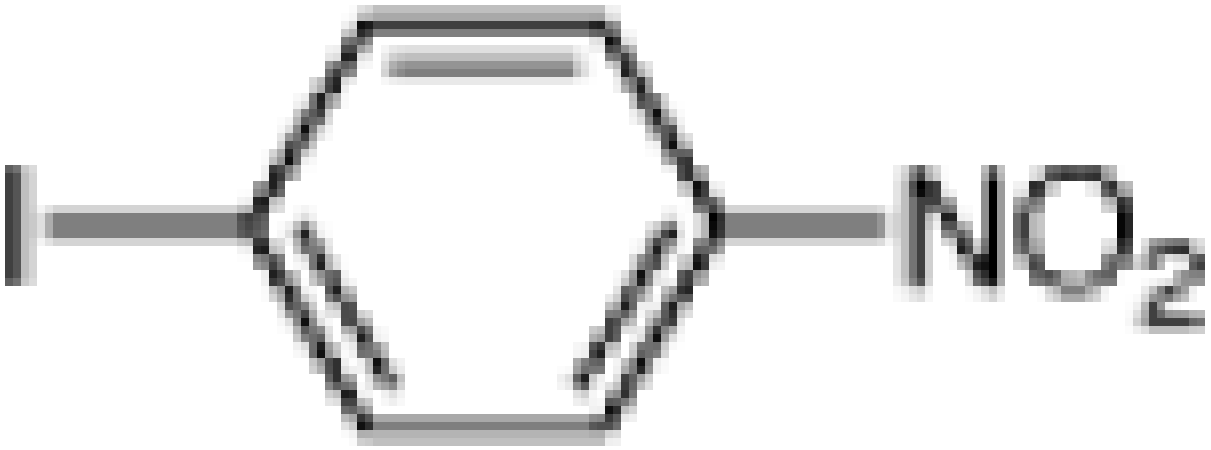
a) *n*-BuLi, Et_2O, - 78 °C, 3
b) CuI, HMPA:THF (1:1), r
c) Electrophile, 3 mol % P
THF, rt, 6 h
d) 1 N HCl, rt, 10 min

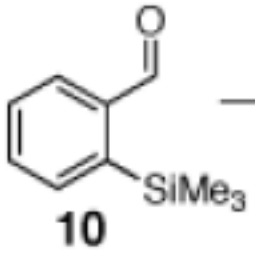
entry	electrophile
2	
3	



10

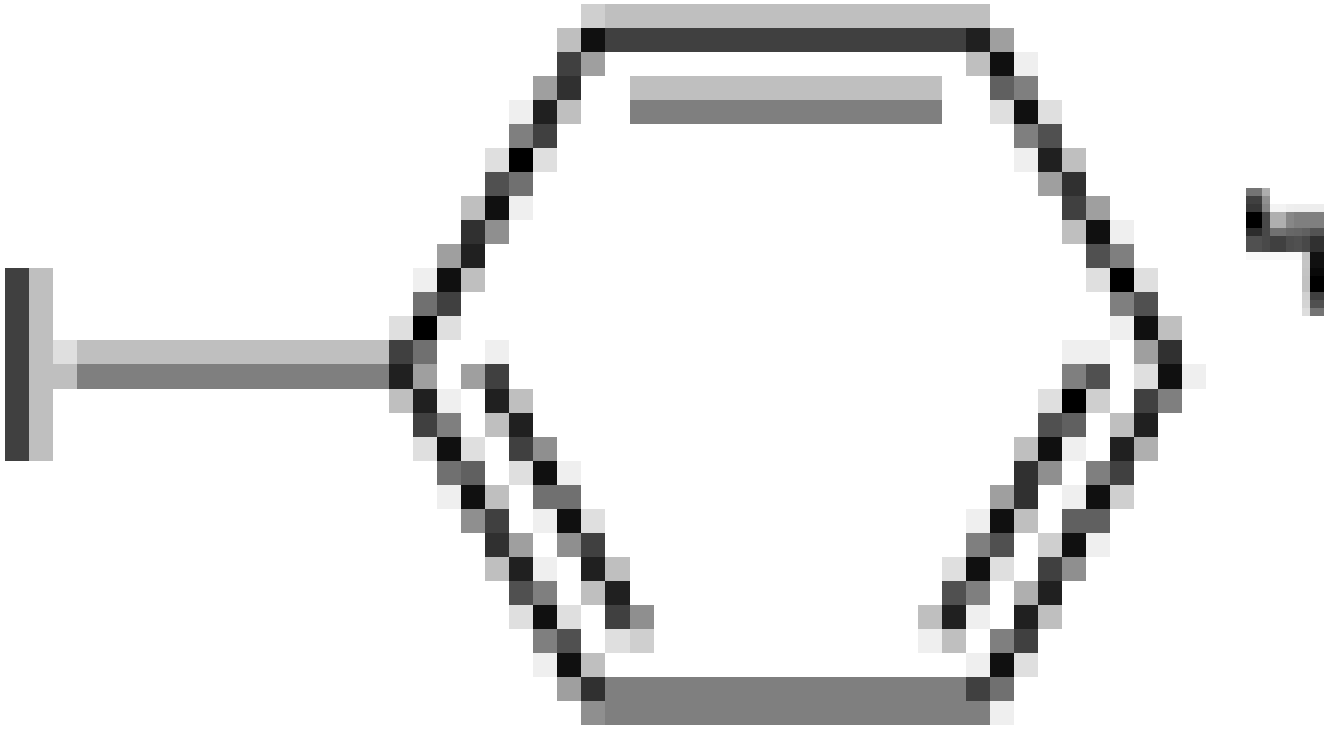
a) *n*-BuLi, Et_2O, - 78 °C, 3
b) CuI, HMPA:THF (1:1), r
c) Electrophile, 3 mol % P
THF, rt, 6 h
d) 1 N HCl, rt, 10 min

entry	electrophile
4	
5	
6	



10

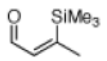
a) *n*-BuLi, Et_2O, - 78 °C, 3
b) CuI, HMPA:THF (1:1), r
c) Electrophile, 3 mol % P
THF, rt, 6 h
d) 1 N HCl, rt, 10 min

entry	electrophile
7	
8	

Conditions: 1.2 equiv *n*-BuLi, 1.2 equiv CuI.

Table 2

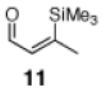
Three-Component Coupling of Linchpin **11** with Various Electrophiles



11

a) *n*-BuLi, Et_2O, –78 °C, 30 min
b) CuI, HMPA:THF (1:1), rt, 30 min
c) Electrophile, rt, 2 h
d) 1 N HCl, rt, 10 min

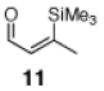
entry	electrophile
1	
2	



11

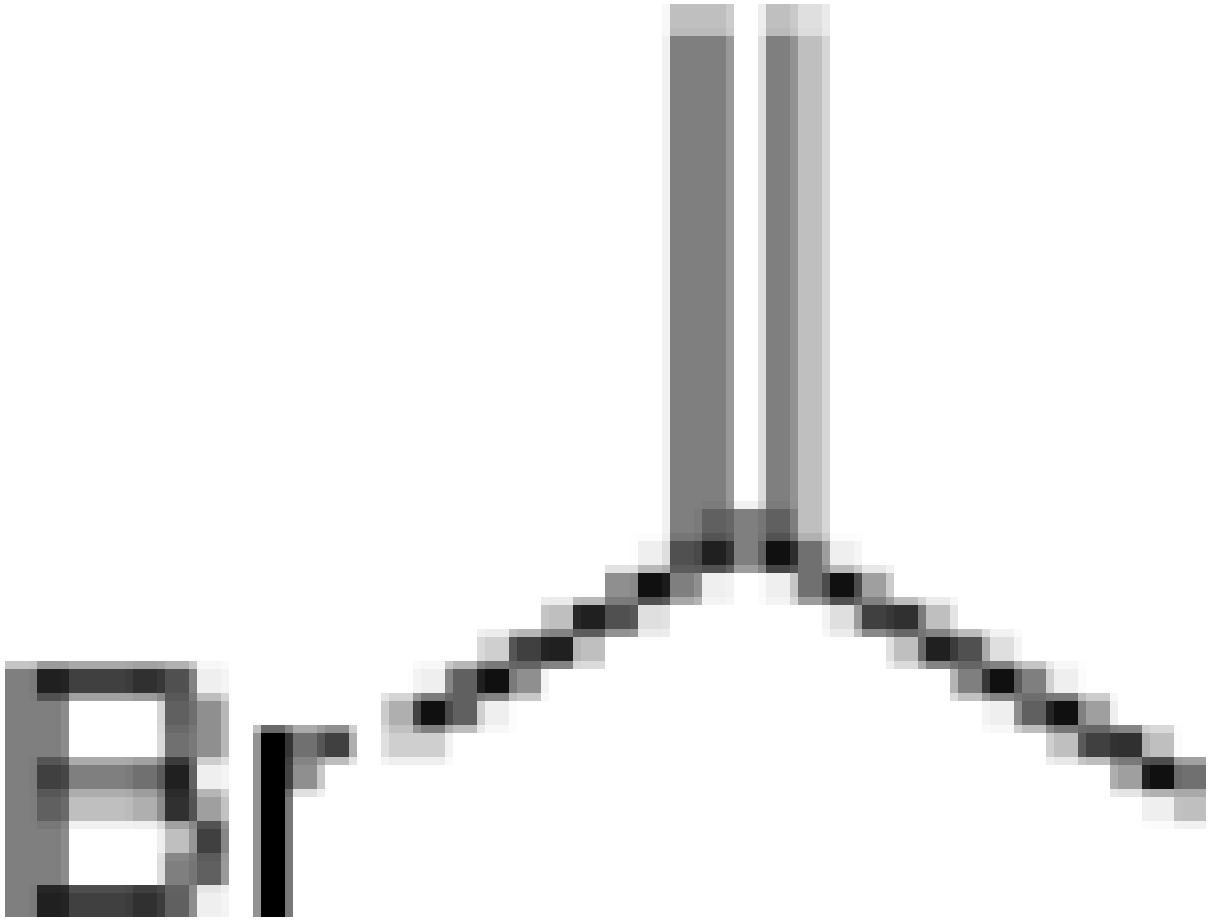
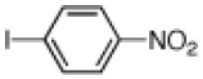
a) *n*-BuLi, Et_2O, –78 °C, 30 min
b) CuI, HMPA:THF (1:1), rt, 30 min
c) Electrophile, rt, 2 h
d) 1 N HCl, rt, 10 min

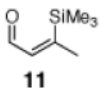
entry	electrophile
3	PhS-SPh
4	Bu_3SnCl



11

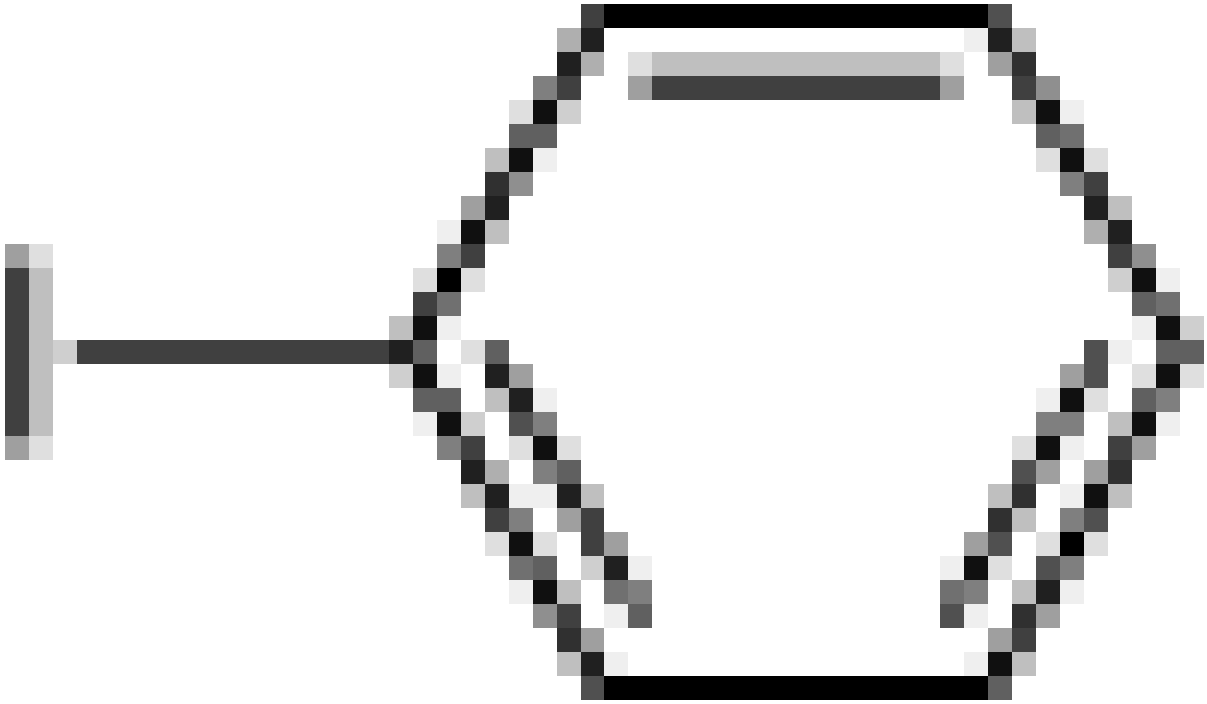
a) *n*-BuLi, Et_2O, –78 °C, 30 min
b) CuI, HMPA:THF (1:1), rt, 30 min
c) Electrophile, rt, 2 h
d) 1 N HCl, rt, 10 min

entry	electrophile
5	
6	



11

a) *n*-BuLi, Et_2O, –78 °C, 30 min
b) CuI, HMPA:THF (1:1), rt, 30 min
c) Electrophile, rt, 2 h
d) 1 N HCl, rt, 10 min

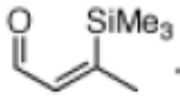
entry	electrophile
7	
8	

Conditions: 1.2 equiv *n*-BuLi, 1.2 equiv CuI.

[a] 3 mol % $Pd(PPh_3)_4$, THF, rt, 6 h.

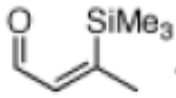
Table 3

Three-Component Coupling of Linchpin **11** with Various Nucleophiles and CCR with Phenyl Iodide



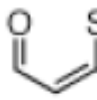
11

entry	nucleophile
1	



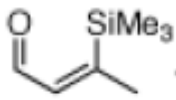
11

entry	nucleophile
2	



11

entry	nucleophile
3	



11

entry	nucleophile
4	

Conditions:

[a] 1 N HCl, rt, 10 min.

[b] TBAF, rt, 1 h.

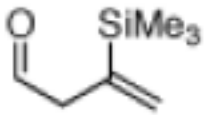
[c] R = Allyl, Allyl bromide, rt, 2 h.

[d] R = Ph, 3 mol % $Pd(PPh_3)_4$, Phenyl iodide THF, rt, 6 h.

[e] No cross-coupling product was obtained due to catalyst poisoning by dithiane.

Table 4

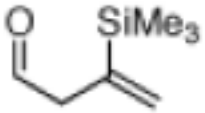
Three-Component Coupling of Linchpin **12** with Various Electrophiles



12

a) *n*-BuLi, Et_2O, –78 °C, 30
b) CuI, HMPA:THF (1:1), rt,
c) Electrophile, rt, 12 h
d) 1 N HCl, rt, 10 min

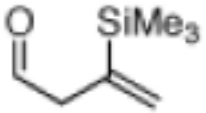
entry	electrophile
1	
2	



12

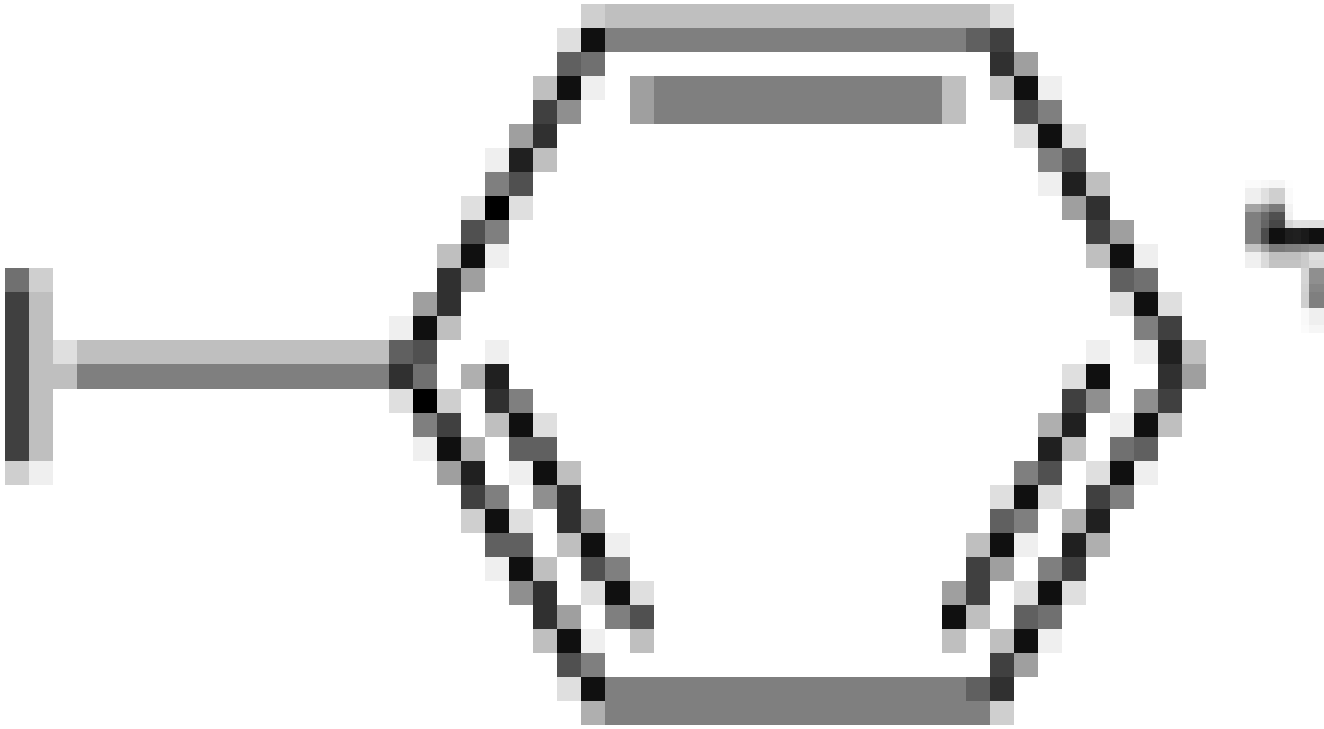
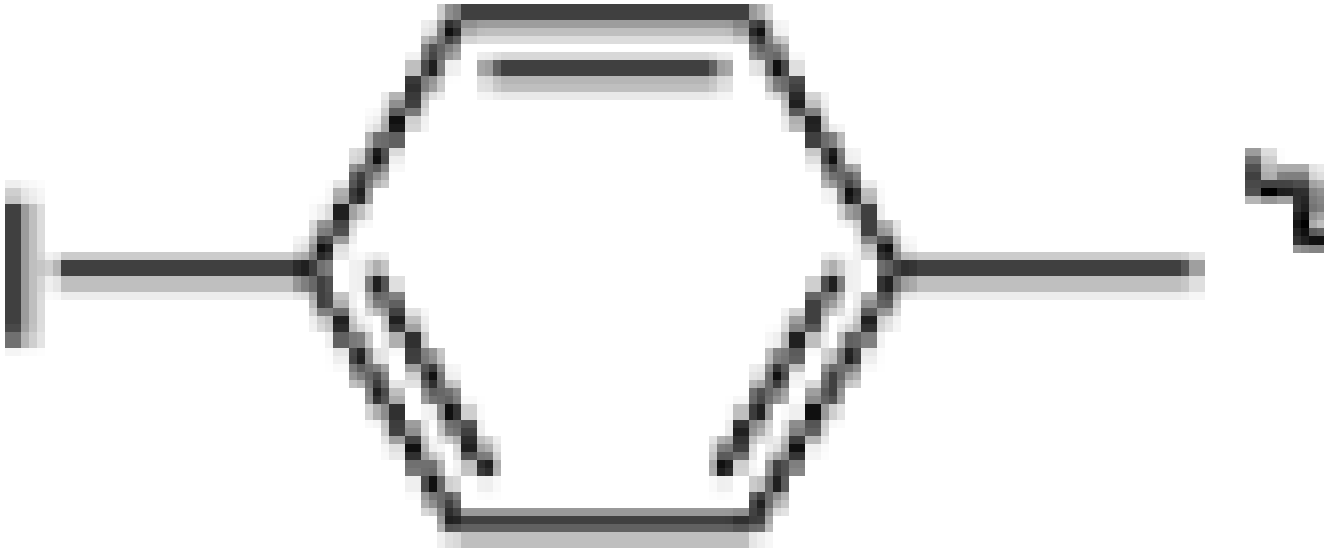
a) *n*-BuLi, Et_2O, –78 °C, 30
b) CuI, HMPA:THF (1:1), rt,
c) Electrophile, rt, 12 h
d) 1 N HCl, rt, 10 min

entry	electrophile
3	PhS-SPh
4	



12

a) *n*-BuLi, Et_2O, –78 °C, 30
b) CuI, HMPA:THF (1:1), rt,
c) Electrophile, rt, 12 h
d) 1 N HCl, rt, 10 min

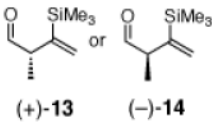
entry	electrophile
5	
6	

Conditions: 2.0 equiv *n*-BuLi, 2.0 equiv CuI.

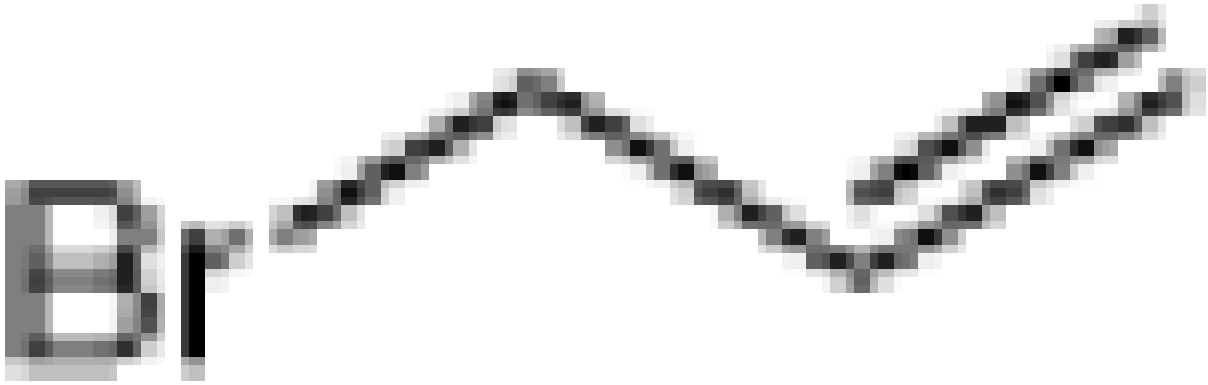
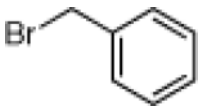
[a] 3 mol % $Pd(PPh_3)_4$, THF, rt, 12 h.

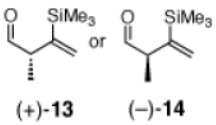
Table 5

Three-Component Coupling of Linchpin (+)-**13** or (−)-**14** with Various Electrophiles

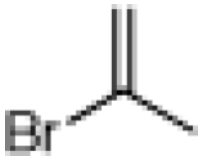
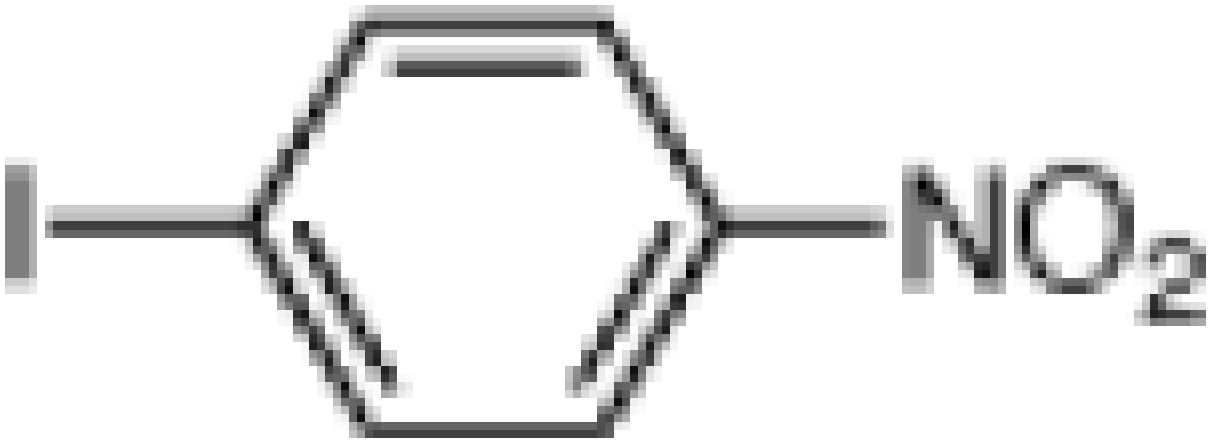


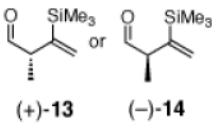
a) *n*-BuLi, Et_2O, –78 °C, 30 mi
b) CuI, HMPA:THF (1:1), rt, 2
c) Electrophile, rt, 12 h
d) 1 N HCl, rt, 10 min

entry	electrophile	R
1		
2		
3	PhS-SPh	
4	Bu_3SnCl	

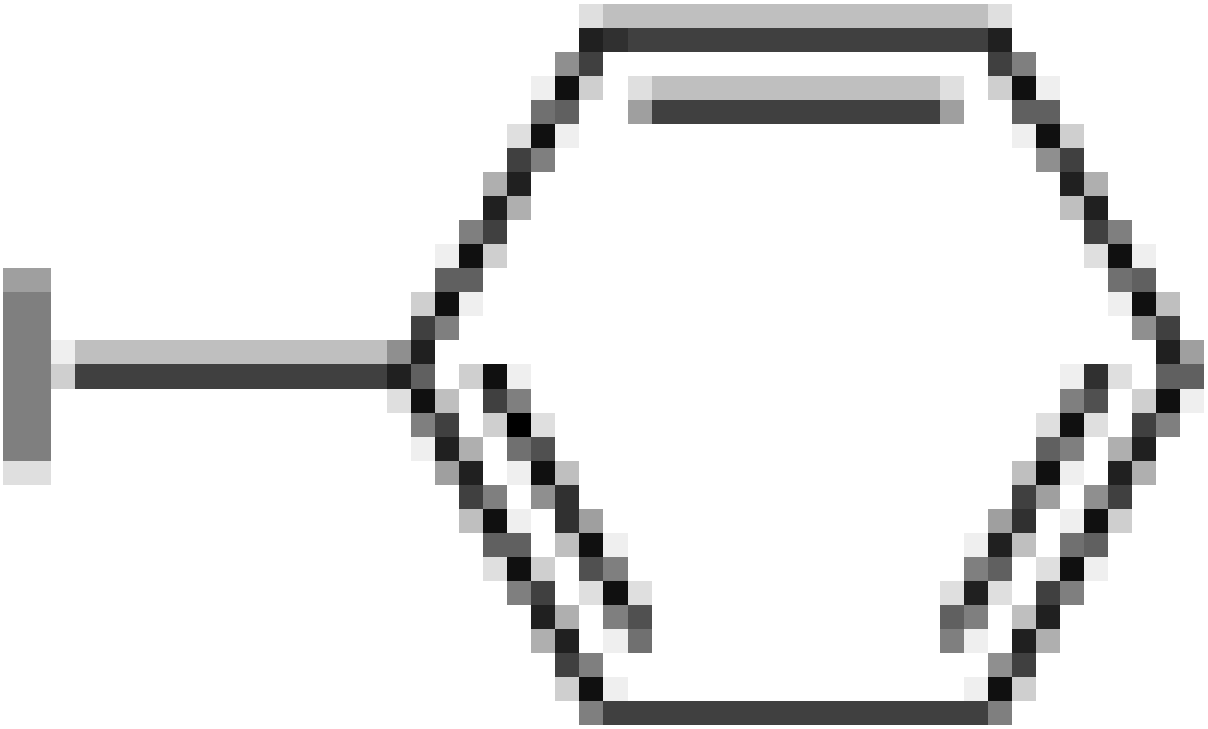


(+)-**13** (–)-**14**

entry	electrophile	R
5		
6		



a) *n*-BuLi, Et_2O, –78 °C, 30 mi
b) CuI, HMPA:THF (1:1), rt, 2
c) Electrophile, rt, 12 h
d) 1 N HCl, rt, 10 min

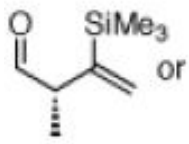
entry	electrophile	R
7		
8		

Conditions: 2.0 equiv *n*-BuLi, 2.0 equiv CuI.

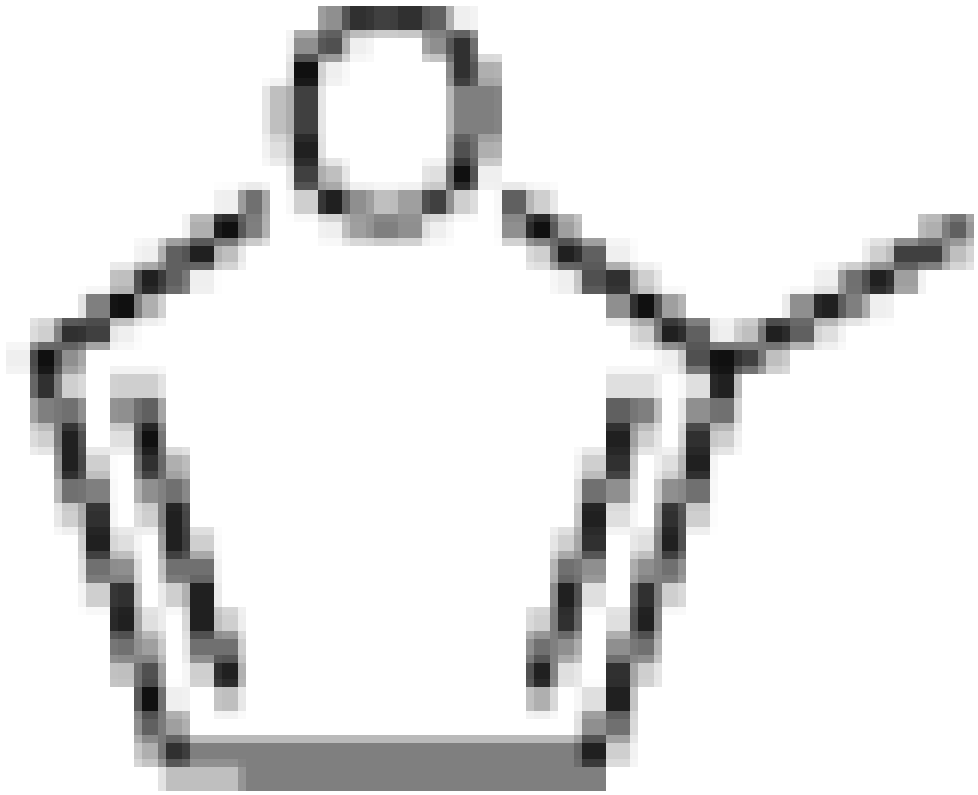
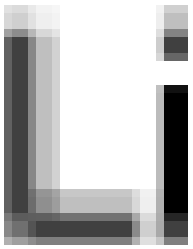
[a] 3 mol % $Pd(PPh_3)_4$, THF, rt, 12 h.

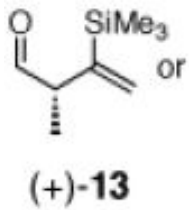
Table 6

Three-Component Coupling of Linchpin (+)-**13** or (−)-**14** with Various Nucleophiles and CCR with Phenyl iodide

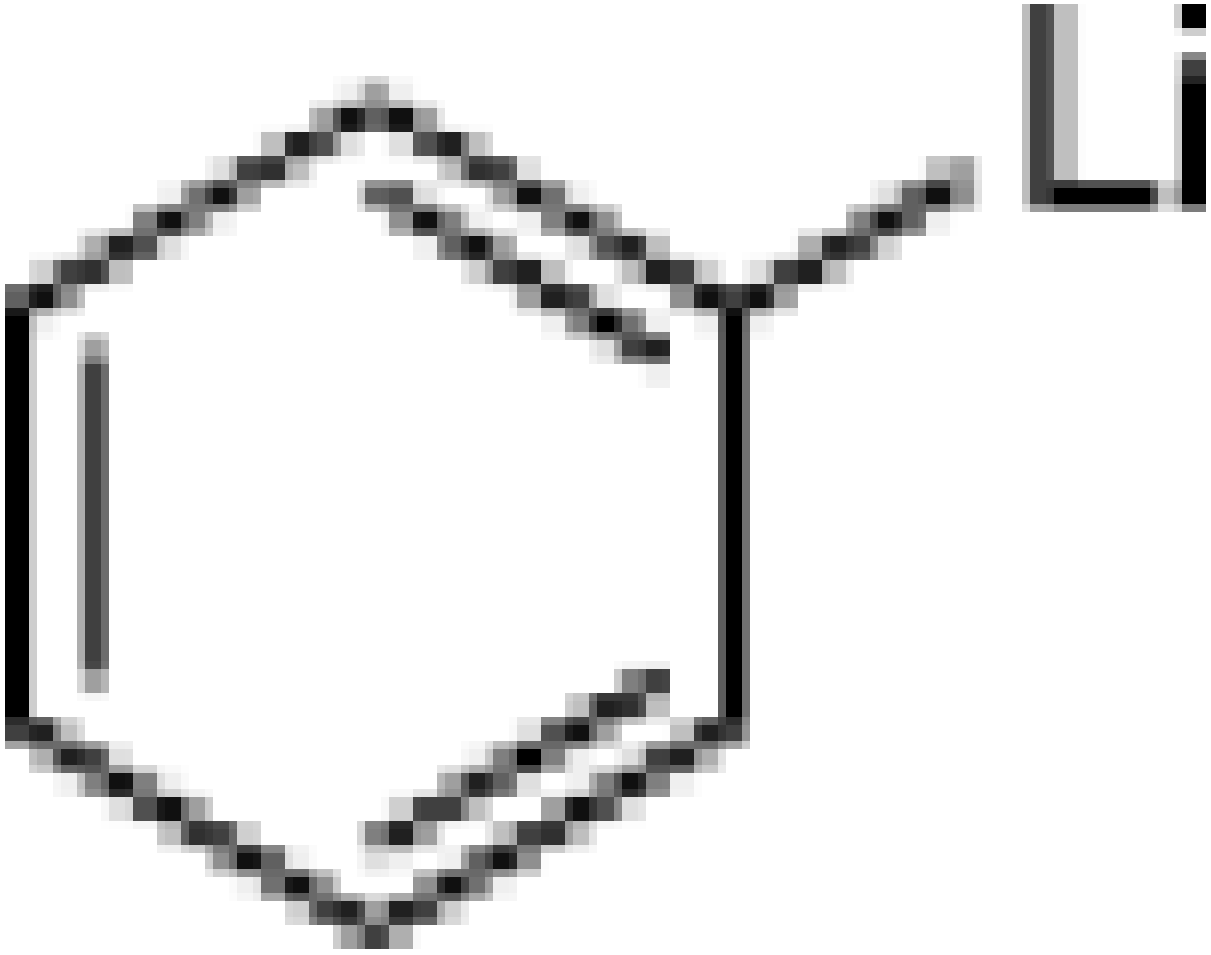


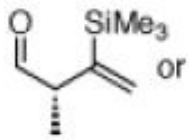
(+)-**13**

entry	nucleophile
1	  



(+)-**13**

entry	nucleophile
2	



(+)-**13**

entry	nucleophile
3	

Conditions:

[a] R = Allyl, Allyl bromide, rt, 12 h.

[b] R = Ph, 3 mol % $Pd(PPh_3)_4$, Phenyl iodide, THF, rt, 12 h.