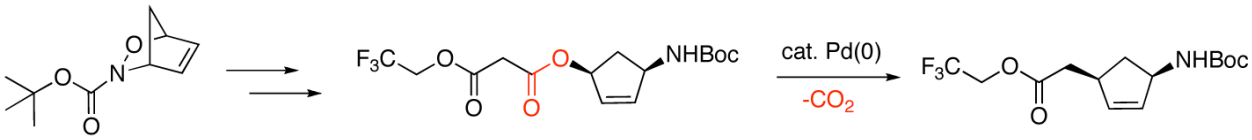
Published in final edited form as:
Org Lett. 2009 September 17; 11(18): 4076–4079. doi:10.1021/ol901518g.

Palladium-Catalyzed Decarboxylative Rearrangements of Allyl 2,2,2-Trifluoroethyl Malonates: Direct Access to Homoallylic Esters

Lawrence P. Tardibono Jr., **Jerod Patzner**, **Cara Cesario**, and **Marvin J. Miller**
Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

Abstract



Homoallylic esters are obtained in a single transformation from allyl 2,2,2-trifluoroethyl malonates by using a Pd(0)-catalyst. Facile decarboxylation of allyl 2,2,2-trifluoroethyl malonates is attributed to a decrease in pK_a compared to allyl methyl malonates. Subsequent reduction of the homoallylic 2,2,2-trifluoroethyl ester provides a (hydroxyethyl)cyclopentenyl derivative that represents a key intermediate in the synthesis of carbocyclic nucleosides. A select allyl 2,2,2-trifluoroethyl malonate undergoes a decarboxylative Claisen rearrangement to provide a regioisomeric homoallylic ester.

Homoallylic esters are embedded in the core structures of several classes of natural products including macrolide polyketides,[1] α-linolenic acid metabolites and derivatives[2] and cyclopentenone prostaglandins.[3] Although homoallylic esters may be synthesized in several steps by functional group manipulation,[2a] direct access to homoallylic esters has been achieved by Krapcho decarboxylation of malonates,[4] addition of vinyl radicals to α,β-unsaturated esters[5] and 1,4-addition of alkenylcopper reagents.[6]

We considered metal-catalyzed decarboxylative allylations as an alternative method to directly prepare homoallylic esters under mild conditions.[7] Although α-cyano, α-nitro, α-keto[8] and α-sulfonyl[9] allyl esters readily undergo Pd(0)-catalyzed decarboxylative rearrangements to afford the corresponding homoallylic derivatives, allyl methyl malonates are much less reactive. Their diminished reactivity is attributed to the less stable methoxyethenolate that forms upon decarboxylation. α,α-Dialkyl allyl methyl malonates require harsh conditions (i. e., 120 °C in DMF) to effect Pd(0)-decarboxylative rearrangements.[8] Diallyl malonates undergo decarboxylative allylation at room temperature, but must possess an aryl group at the α-position.[10] To our knowledge, Pd(0)-decarboxylative rearrangements of α,α-unsubstituted allyl alkyl malonates have not been reported. In order to achieve decarboxylation, we envisioned replacement of the allyl methyl malonate with an allyl 2,2,2-trifluoroethyl malonate. The strong electron-withdrawing ability of the trifluoroethyl group would improve the stability of the transient alkoxyethenolate and promote decarboxylation. Herein, we disclose that α,α-unsubstituted allyl 2,2,2-trifluoroethyl malonates are suitable substrates for Pd(0)-catalyzed decarboxylative allylations and provide desired homoallylic 2,2,2-trifluoroethyl esters in high yields.

mmiller1@nd.edu.

Our group has previously reported Pd(0)-catalyzed allylic alkylations with cycloadduct **3**[11] and related substrates as key steps en route to targeted carbocyclic nucleosides.[12] In order to access carbonucleoside targets 5′-homocarbovir **1b**[13] and 5′-homoaristeromycin **2b**,[14] we required a reliable method to install the requisite 5′-hydroxyethyl side chain. We envisioned a Pd(0) decarboxylative rearrangement to afford an α-allyl ester and subsequent reduction to the (hydroxyethyl)cyclopentyl core structure. Further elaboration would furnish **1b** and **2b** (Figure 1).

As a model system to explore palladium catalyzed decarboxylative allylation of 1,4-*syn* disubstituted cyclopentenes, allyl β-keto ester **5** was synthesized in two steps from cycloadduct **3** (Scheme 1).[15,16] Allyl β-keto esters are reliable substrates that undergo Pd(0)-catalyzed decarboxylative rearrangements under mild conditions.[8,17] The mechanism proceeds through oxidative addition to give a metal β-keto carboxylate/π-allyl system. Upon decarboxylation, nucleophlic attack by the resulting enolate affords ketone products. When allyl β-keto ester **5** was treated with Pd(0), ketone **6** was isolated in 65% yield as the exculsive product with complete diastereo- and regiocontrol. This initial result demonstrated that appropriately functionalized cyclopentenes derived from **4** are suitable substrates for decarboxylative allylations.

Replacement of the allyl β-keto ester group with an allyl methyl malonate system would provide access to a versatile homoallylic ester sidechain. The ester could be converted to an alcohol or aldehyde and give access to key intermediates in the synthesis of carbonucleosides. Cyclopentenol **4** was coupled to methyl malonate to give allyl methyl malonate **7** in 91% yield. Exposure of **7** to various palladium sources ($Pd(OAc)_2$, $Pd(dba)_2$, $Pd_2(dba)_3{\cdot}CHCl_3$) and temperatures resulted in no reaction and recovery of starting material (Scheme 2).[18]

In an attempt to increase stabilization of the anionic intermediate that is formed upon decarboxylation, acids **10a** and **10b** were coupled with cyclopentenol **4** to form allyl 2,2,2-trichloroethyl malonate **11a** and allyl 2,2,2-trifluoroethyl malonate **11b** in high yields, respectively (Scheme 3). Although trichloroethyl derivative **11a** did not undergo decarboxylative rearrangement in the presence of $Pd(dba)_2$ and PPh_3, trifluoroethyl substrate **11b** provided homoallylic ester **12b** under similar reaction conditions with complete diastereo- and regiocontrol. The electron withdrawing effect of the trifluoroethyl group plays a significant role in accelerating the decarboxylative rearrangement.

Next, we turned our attention to optimizing the reaction conditions for formation of α-allyl ester **12b** (Table 1). Accordingly, a series of palladium sources and ligands were investigated with DMF as solvent. The combination of $Pd(dba)_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) emerged as the optimal source of Pd(0). However, heating the reaction mixture at 100 °C in DMF was undesirable and removal of DMF complicated the purification and isolation process. Several solvents were explored at lower temperatures and ultimately THF proved to be optimal (Table 1, entry 7) and a yield of 82% was obtained.[19,20] A control reaction (Table 1, entry 8) in the absence of Pd(0) and ligand was also performed to confirm that the process was not thermally driven. Decomposition of malonate **11b** was not observed after stirring at 145 °C in DMF for 16 h. The retention of the 1,4-*syn* stereochemistry of **12b** was expected due to the double inversion via the palladium π-allyl system. The 1,4-*syn* stereochemistry of ester **12b** was confirmed by ^1H NMR. A characteristic coupling pattern (J = 6.5, 6.5, 13.5 Hz and J = 7.8, 7.8, 13.5 Hz) was observed for the diastereotopic methylene protons in the cyclopentene core.[21]

With a reliable method to 1,4-*syn* cyclopentene derivative **12b** established, we turned our attention to the synthesis of 1,2-*syn* cyclopentene derivative **13** by employing a decarboxylative Claisen rearrangement. The base catalyzed [3,3]-sigmatropic rearrangement-decarboxylation

of tosylmalonic mono(allylic) esters has recently been reported.[22] While substrate **11b** does not have the additional electron withdrawing Ts group at the α-position, it was envisioned that the increased electron withdrawing effects of the trifluoroester would allow for the rearrangement to occur. Malonate **11b** was subjected to *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc in anhydrous toluene at 100 °C (Scheme 4).[23] Unfortunately, partial decomposition occurred and product **13** was not detected. This result was not unexpected considering the steric bulk imparted by the Boc-protected amine in pseudo-boat transition state **TS-1**.

In order to avoid a sterically hindered transition state, we synthesized 1,4-*trans* diastereomer **14** as a substrate for the decarboxylative Claisen rearragement. Alcohol **4** was subjected to Mitsunobu conditions in the presence of acid **10b** to afford 1,4-*trans* malonate **14** (Scheme 5). Malonate **14** was exposed to the decarboxylative Claisen rearrangement conditions and ester **15** was obtained in 52% yield. The unfavorable boat-like 6-membered transtion state **TS-2** could have contributed to the relatively low yield. Malonate **14** also underwent efficient Pd(0)-catalyzed decarboxylative rearrangement to 1,4-*trans* cyclopentene **16** (Scheme 6).[20] The stereochemistry of **15** and **16** was confirmed by analyses of the COSY and/or ROESY NMR spectra.

Finally, allyl 2,2,2-trifluoroethyl malonate (-)-**11b** was synthesized from the readily available aminocyclopentenol (-)-**4**[24] and converted to ester (-)-**12b**. Treatment with diisobutylaluminum hydride provided alcohol (-)-**17** in 85% yield (Scheme 7). Alcohol (-)-**17** represents a key intermediate towards the synthesis of (-)-5′-homocarbovir **1b** and (-)-5′-homoaristeromycin **2b**.

In summary, allyl 2,2,2-trifluoroethyl malonates undergo efficient Pd-catalyzed decarboxylative allylation. Installation of the trifluoroethyl group resulted in improved stabilization of the reactive carbanion intermediate. Simple esters and trichloroethyl ester groups were not effective. We have also identified substrate **14** as a new system for the decarboxylative Claisen rearrangement. Alcohol (-)-**17** is currently being used as a key intermediate to synthesize carbocyclic nucleosides. Those investigations will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge Nonka Sevova (University of Notre Dame) for mass spectroscopic analyses, Dr. Jaroslav Zajicek (University of Notre Dame) for NMR assistance, and Dr. Jed Fisher (University of Notre Dame) for helpful discussions. We acknowledge the University of Notre Dame and NIH (GM 068012 and GM 075885) for support of this work.

References

(1). Sheehan LS, Lill RE, Wilkinson B, Sheridan RM, Vousden WA, Kaja AL, Crouse GD, Gifford J, Graupner PR, Karr L, Lewer P, Sparks TC, Leadlay PF, Waldron C, Martin CJ. J. Nat. Prod 2006;69:1702. [PubMed: 17190446]

(2). (a) Nonaka H, Wang Y-G, Kobayashi Y. Tetrahedron Lett 2007;48:1745. (b) Pinot D, Guy A, Fournial A, Balas L, Rossi J-C, Durand T. J. Org. Chem 2008;73:3063. [PubMed: 18351775]

(3). Negishi M, Katoh H. Prostag. Oth. Lipid M 2002;68-69:611.

(4). Acharya H, Kobayashi Y. Tetrahedron 2006;62:3329.

(5). (a) Miura K, Itoh D, Hondo T, Hosomi A. Tetrahedron Lett 1994;35:9605. (b) Foubelo F, Lloret F, Yus M. Tetrahedron 1994;50:6715.

(6). Cahiez G, Venegas P, Tucker CE, Majid TN, Knochel P. J. Chem. Soc., Chem. Commun 1992;19:1406.

(7). For a review on decarboxylative allylations, see:(a) Tunge JA, Burger EC. Eur. J. Org. Chem 2005:1715. (b) Dai LX, You SL. Angew. Chem. Int. Ed 2006;45:5246.

(8). Tsuji J, Yamada T, Minami I, Yuhara M, Nisar M, Shimizu I. J. Org. Chem 1987;52:2988.

(9). Weaver J, Tunge JA. Org. Lett 2008;10:4657. [PubMed: 18785744]

(10). Imao D, Itoi A, Yamazaki A, Shirakura M, Ohtoshi R, Ogata K, Ohmori Y, Ohta T, Ito Y. J. Org. Chem 2007;72:1652. [PubMed: 17261068]

(11). Mulvihill MJ, Surman MD, Miller MJ. J. Org. Chem 1998;63:4874.

(12). (a) Jiang MX-W, Jin B, Gage JL, Priour A, Savela G, Miller MJ. J. Org. Chem 2006;71:4164. [PubMed: 16709056] (b) Li F, Brogan JB, Gage JL, Zhang D, Miller MJ. J. Org. Chem 2004;69:4538. [PubMed: 15202916]

(13). For total synthesis of (±)-5′-homocarbovir, see:Rhee H, Yoon D, Jung ME. Nucleosides, Nucleotides Nucleic Acids 2000;19:619. [PubMed: 10843497]

(14). For total synthesis of (-)-5′-homoaristeromycin, see:(a) Roberts SM, Jones MF. J. Chem. Soc., Perkin Trans. I 1988:2927. (b) Yang M, Schneller SW. Bioorg. Med. Chem. Lett 2005;15:149. [PubMed: 15582429]

(15). For N-O bond reductions of cylcloadducts, see:Cesario C, Tardibono L, Miller MJ. J. Org. Chem 2009;74:448. [PubMed: 19053586]

(16). Diketene reaction conditions adapted from a procedure found in:Collado I, Mazón A, Espinosa JF, Blanco-Urgoiti J, Schoepp DD, Wright RA, Johnson BG, Kingston AE. J. Med. Chem 2002;45:3619. [PubMed: 12166935]

(17). Burger EC, Tunge JA. Org. Lett 2004;6:4113. [PubMed: 15496112]

(18). For a detailed table of reaction conditions, see Supporting Information.

(19). The reaction is performed under anhydrous conditions in a sealed tube. High yields (76%) were observed on 1.5 mmol scale. Decreased yields (61%) were observed on 6 mmol scale.

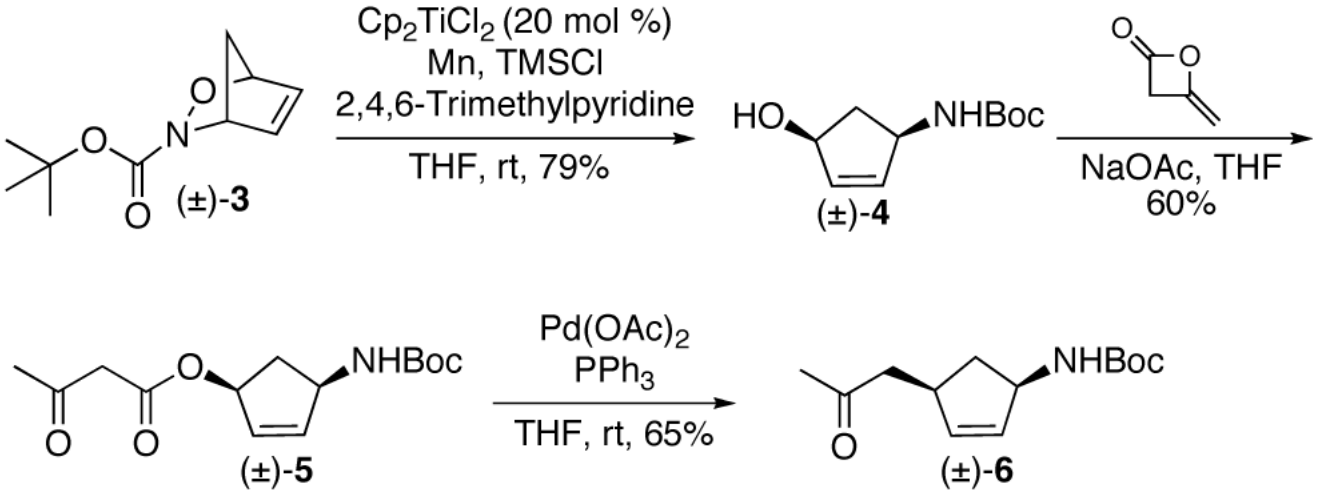
(20). Crude reaction mixture was analyzed by ^{1}H NMR and showed complete consumption of the allyl 2,2,2-trifluoroethyl malonate and the formation of a single product with complete diastereo- and regiocontrol.

(21). For a brief discussion of coupling constants of 1,4-disubstituted cyclopentenes, see:Mulvihill MJ, Surman MD, Miller MJ. J. Org. Chem 1998;63:4874.

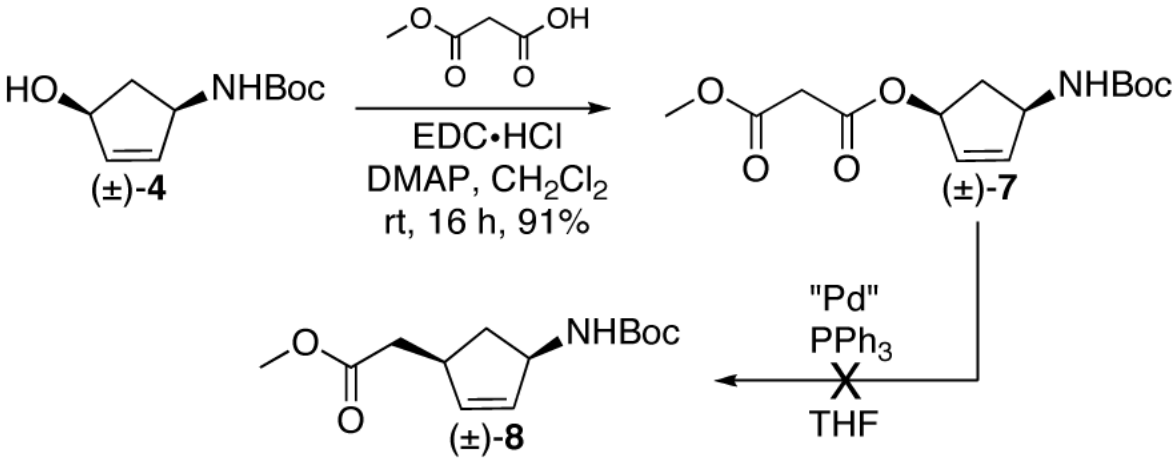
(22). Craig D, Grellepois F. Org. Lett 2005;7:463. [PubMed: 15673265]

(23). For mechanistic discussions of the decarboxylative Claisen rearrangement, see:(a) Bourgeois D, Craig D, King NP, Mountford DM. Angew. Chem., Int. Ed 2005;44:618. (b) Craig D, Grellepois F, White AJP. J. Org. Chem 2005;70:6827. [PubMed: 16095302]

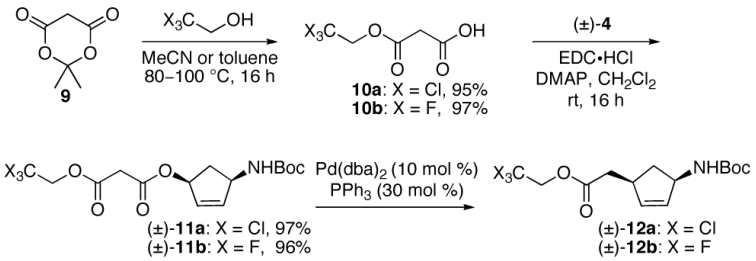
(24). Mulvihill MJ, Gage JL, Miller MJ. J. Org. Chem 1998;63:3357.



Scheme 1.



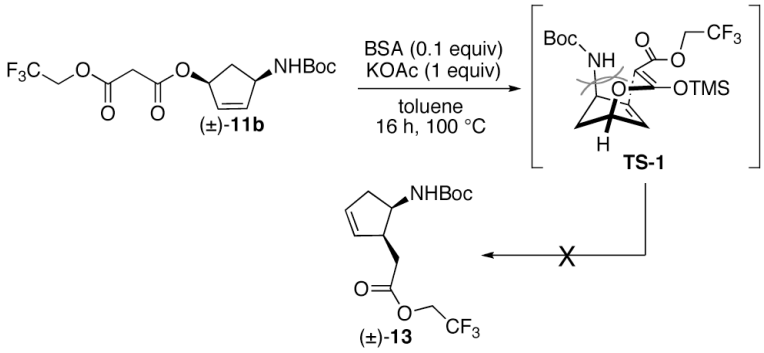
Scheme 2.



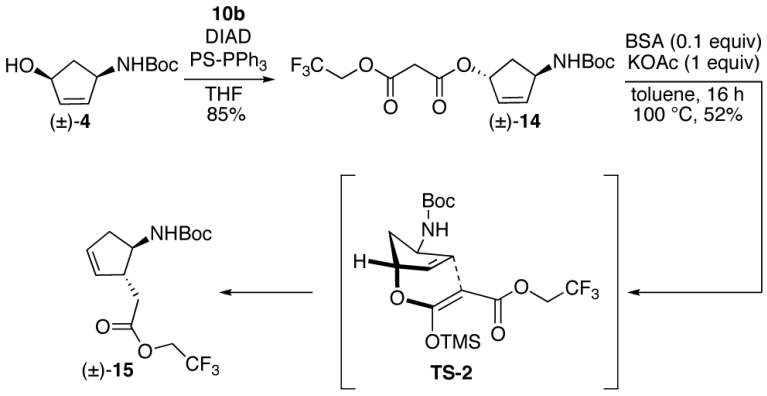
entry	substrate	solvent	temp	time	isolated yield
1	**11a**	THF	75 °C	8 h	0%[a]
2	**11b**	THF	50 °C	8 h	37%
3	**11b**	DMF	100 °C	5 h	53%

[a] Starting material was recovered.

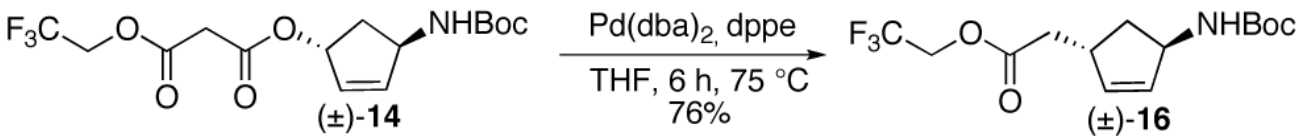
Scheme 3.



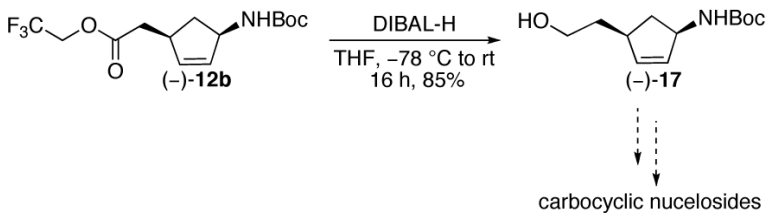
Scheme 4.



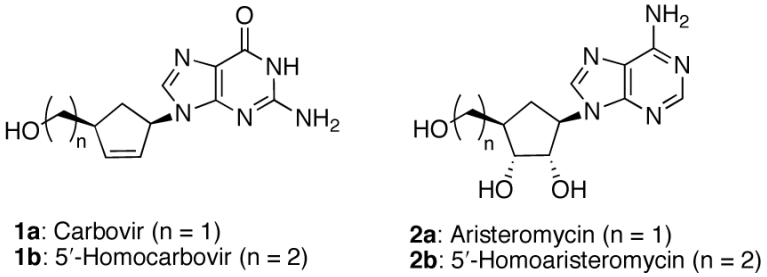
Scheme 5.



Scheme 6.



Scheme 7.



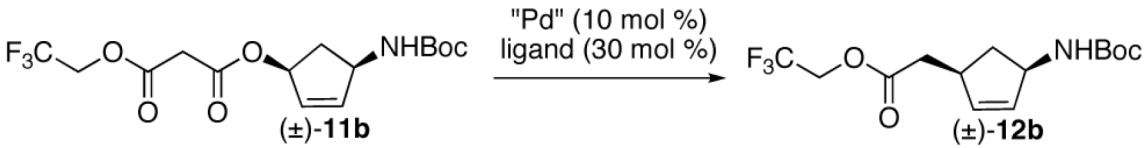
1a: Carbovir (n = 1)
1b: 5′-Homocarbovir (n = 2)

2a: Aristeromycin (n = 1)
2b: 5′-Homoaristeromycin (n = 2)

Figure 1.
Carbonucleoside Target Molecules.

Table 1

Selected Reaction Conditions for Optimization Studies



entry	Pd/ligand	solv.	temp	time	isolated yield
1	$Pd(OAc)_2$ PPh_3	DMF	100 °C	5 h	40%
2	$Pd_2(dba)_3{\cdot}CHCl_3$ PPh_3	DMF	100 °C	5 h	40%
3	$Pd(dba)_2$ $P(OPh)_3$	DMF	100 °C	8 h	0%[a]
4	$Pd(dba)_2$ *rac*-BINAP	DMF	100 °C	4 h	51%
5	$Pd(dba)_2$ PS-PPh_3	DMF	100 °C	4 h	56%
6	$Pd(dba)_2$ dppe	DMF	100 °C	4 h	60%
7	$Pd(dba)_2$ dppe [b]	THF	75 °C	6 h[c]	82%
8	no palladium no ligand	DMF	145 °C	16 h	0%[a]

[a] Starting material was recovered.

[b] Reaction conducted with 5 mol % $Pd(dba)_2$ and 15 mol % dppe resulted in 50% conversion to product (by ^1H NMR integration) after 6 h.

[c] Longer reactions time (16 h) resulted in lower yield (53%).