Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3751–3754

TETRAHEDRON: *ASYMMETRY*

The asymmetric synthesis of cyclopentane derivatives by palladium-catalyzed coupling of prochiral alkylboron compounds

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Received 31 August 1998; accepted 21 September 1998

Abstract

Treatment of the prochiral triflate **2a** with $Pd_2(dba)_3 \cdot CHCl_3$, (*S*)-(*R*)-BPPFOAc and K_2CO_3, in THF at 40°C, gave the cyclopentane derivative **10** in 58% yield and in 28% ee after oxidative work-up and benzoylation. Moreover, reaction of the prochiral triflate **2c** with $Pd_2(dba)_3 \cdot CHCl_3$, (*S*)-(*R*)-PPFA and K_2CO_3, in THF at 40°C, afforded the cyclopentane derivative **3b**, with a quaternary carbon center, in 42% yield and in 31% ee after oxidative work-up.

Palladium-catalyzed coupling reactions of organic halides or organic triflates with organoboron compounds, generally referred to as Suzuki–Miyaura reactions,[1] are powerful methods for various carbon–carbon bond-forming reactions. However, only limited attention has been paid to an asymmetric Suzuki–Miyaura reaction,[2] which would provide an efficient method for the synthesis of a variety of optically active carbon centers that would be difficult to obtain by other methods. Using our experience in the field of palladium-catalyzed asymmetric Heck reactions,[3] we focused on an asymmetric design of a palladium-catalyzed Suzuki–Miyaura reaction. In this paper we report a catalytic asymmetric synthesis of cyclopentane derivatives by palladium-catalyzed coupling of prochiral alkylboron compounds.

Our basic strategy involves enantiotopic group selective ring closure of the prochiral triflates **2a** and **2c**, and bromide **2b**. This closure, catalyzed by a palladium complex with an asymmetric ligand, would lead to the optically active cyclopentane derivatives **3a** and **3b** after oxidative work-up. Prochiral substrates **2a**, **2b** and **2c** were expected to be readily prepared from the corresponding substrates, with two olefinic moieties, using hydroboration (Scheme 1). Initially, the feasibility of an asymmetric coupling of **2a** promoted by a palladium complex with an asymmetric ligand, was examined in detail, and this allowed the development of an efficient synthetic route to **1a** (shown in Scheme 2). Thus, ethyl acetoacetate **4** was converted to the alkenyl triflate **1a**, which possesses two olefinic moieties, in 40% overall yield for the three steps. Hydroboration of **1a** was carried out using 2.5 mol equivalents of 9-BBN (THF, 40°C, 1 h), because this convenient reagent readily allowed the preparation of a variety of functionalized alkylboron derivatives from their corresponding terminal alkenes. The resulting THF solution of the

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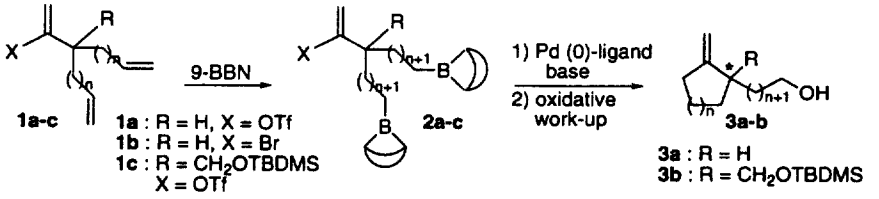
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00386-3

alkylboron compound **2a** was degassed three times (freeze–pump–thaw cycle method (FPT method)) before coupling was attempted. After several attempts at coupling, it was found that the use of the $Pd_2(dba)_3 \cdot CHCl_3$ complex as a palladium source, and K_2CO_3 as a base were the most effective. Many asymmetric couplings were carried out as follows.

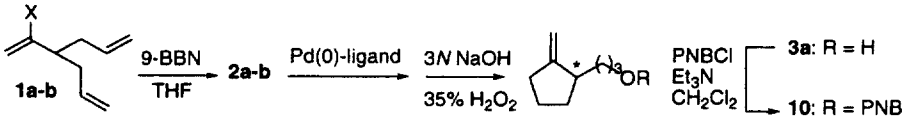


Scheme 1.

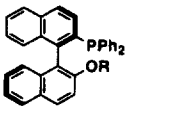
A stirred suspension of $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol%), an asymmetric ligand (20 mol%) and K_2CO_3 (5 mol equiv.), in THF, was degassed three times (FPT method), and the suspension was stirred at 40°C for 1 h. To this suspension was added the degassed THF solution of **2a**, and the resulting reaction mixture was stirred at 40°C for 12 h. Oxidative work-up with 3 N NaOH and 35% H_2O_2, at 0°C, gave the cyclopentane derivative **3a**. As shown in Table 1, the use of (*R*)-BINAP gave no product **3a** (entry 1, Table 1). However, the use of monodentate ligands[4] such as (*R*)-MOP(OCH_3), (*R*)-MOP(*O*-*i*-Pr) and (*R*)-MOP(OH), resulted in the formation of **3a** in good yields albeit with low ees (up to 14% ee) (entries 2 and 3, Table 1). To the best of our knowledge, this is the first reported example of an intramolecular asymmetric Suzuki–Miyaura reaction. The use of the bidentate ligand (*S*)-(*R*)-BPPFOAc[5] afforded the desired product **10** in 58% yield and 28% ee (entry 5, Table 1).

In an attempt to further improve the above result, solvent effects were investigated (CH_2Cl_2 or DMF were used); however, THF was found to be the best solvent for the present asymmetric Suzuki–Miyaura reaction. The ee of **3a** was determined at the stage of the benzonate **10** by HPLC analysis using a chiral stationary column (Chiralpak OJ, hexane:isopropanol 5000:1). We further continued to improve an intramolecular asymmetric Suzuki–Miyaura reaction. The precise mechanism for the coupling between

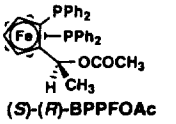
Table 1
Asymmetric cross-coupling reaction of alkenyl triflate **2a** and bromide **2b**[a]



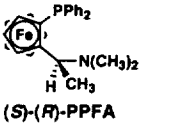
entry	substrate (X=OTf, Br)	ligand	base	solvent	yield of **10** (%)	ee of **10** (%) (abs. config)
1	OTf	(*R*)-BINAP	K_2CO_3	THF	NR	
2	OTf	(*R*)-MOP(OMe)	K_2CO_3	THF	67	14(*S*)
3	OTf	(*R*)-MOP(OH)	K_2CO_3	THF	59	6(*S*)
4	OTf	(*S*)-(*R*)-PPFA	K_2CO_3	THF	48	20(*S*)
5	OTf	(*S*)-(*R*)-BPPFOAc	K_2CO_3	THF	58	28(*R*)
6	OTf	(*S*)-(*R*)-BPPFOAc	K_2CO_3	CH_2Cl_2	33	8(*R*)
7	OTf	(*S*)-(*R*)-BPPFOAc	K_2CO_3	DMF	17	12(*R*)
8	OTf	(*S*)-(*R*)-BPPFOAc	Cs_2CO_3	THF	50	10(*R*)
9[b]	OTf	(*S*)-(*R*)-BPPFOAc	*i*-Pr_2NEt	THF	60	4(*R*)
10	Br	(*S*)-(*R*)-BPPFOAc	K_2CO_3	THF	41	10(*S*)
11	Br	(*R*)-BINAP	K_2CO_3	THF	trace	
12	Br	(*R*)-BINAs[c]	K_2CO_3	THF	37	0
13	Br	(*R*)-BINAPAs[d]	K_2CO_3	THF	10	2(*R*)



(*R*)-MOP(OR)



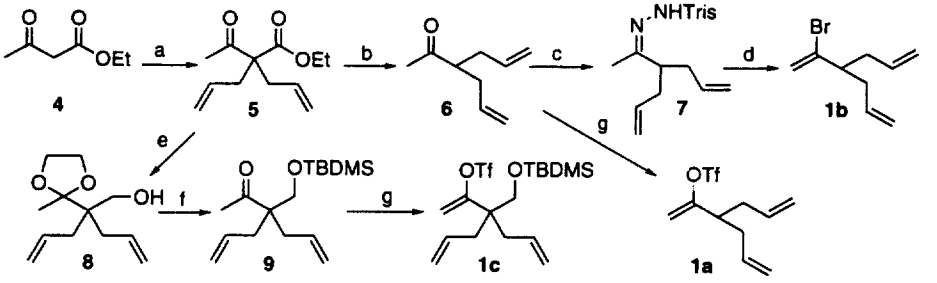
(*S*)-(*R*)-BPPFOAc



(*S*)-(*R*)-PPFA

a: Unless otherwise stated, reactions were carried out by using 10 mol % $Pd_2(dba)_3$, 20 mol % ligand 5 mol equiv base, 40 °C. b: 3 equiv *i*-Pr_2NEt was used, c: See ref. 12, d: See ref. 13, NR: No reaction.

organic triflates or organic halides with organoboron compounds, particularly the transmetallation step, has not been fully elucidated,[1] and so we also examined the use of an alkenyl bromide with two olefinic moieties for an intramolecular asymmetric coupling. As shown in Scheme 2, the bromide **1b** was prepared from **6**, by a modified Shapiro reaction, using 2,4,6-triisopropylbenzenesulfonyl hydrazide.[6] However, as shown in Table 1 (entries 10–13), less satisfactory results were obtained for the asymmetric coupling.

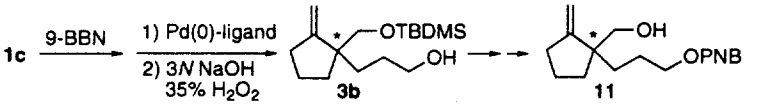


Scheme 2. (a) Allyl chloride (2.5 equiv.), $BnEt_3NCl$, KOH_{aq}, benzene, rt, 65%. (b) LiCl, DMF, reflux, 90%. (c) 2,4,6-Triisopropylsulfonyl hydrazide, MeOH, H^+, 70%. (d) (1) 2 Equiv. BuLi, −78°C–0°C, TMEDA/pentane, (2) $BrCH_2CH_2Br$, 0°C, 50%. (e) (1) Ethylene glycol, TsOH, benzene, reflux, (2) $LiAlH_4$, Et_2O, 2 steps 90%. (f) (1) TBDMSCl, imidazole, DMF, (2) $FeCl_3 \cdot SiO_2$, acetone, 2 steps 95%. (g) KHMDS, $PhNTf_2$, THF, −78°C, 66–68%

Although the highest ee of **3a** was still low, we next investigated the catalytic asymmetric construction of a quaternary carbon center[7] using the alkenyl triflate **1c**. The requisite triflate **1c** was prepared as shown in Scheme 2, and, after hydroboration under the standard conditions, an intramolecular asymmetric coupling was attempted using the resulting organoboron compound **2c**. The results are summarized in Table 2. When the reaction was carried out using (*S*)-(*R*)-BPPFOAc as the asymmetric ligand, the coupling proceeded smoothly giving the cyclopentane derivative **3b** after oxidative work-up in 65% yield but only 2% ee. However, it was found that the use of (*R*)-BINAP monooxide,[8] prepared in situ, resulted in the formation of **3b** in 60% yield and 16% ee. In an attempt to improve this result, ligand effects were further examined. (*S*)-(*R*)-PPFA[9] proved to be the best ligand for this asymmetric coupling reaction, giving the coupling product **3b** in 31% ee and 42% yield. The ee of **11** was determined by HPLC analysis using a chiral stationary column (Chiralpak OJ, hexane:isopropanol 9:1).

The absolute configuration of coupling products **3a** and **3b** could be easily determined as follows (Scheme 3). The product **3a** was converted into the corresponding tosylate, and then further transformed into the known alkyl ketone **13**,[10] by a substitution reaction with a copper reagent followed by ozonolysis

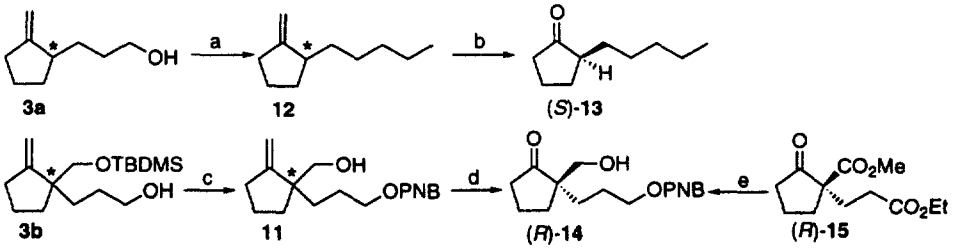
Table 2
Asymmetric cross-coupling reaction of alkenyl triflate **2c**[a]



entry	ligand	time (h)	yield of **3b** (%)	ee of **11** (%) (abs. config)
1	(*R*)-BINAP	24	trace	
2	(*R*)-BINAs	24	NR	
3	(*R*)-BINAPAs	12	57	11(*S*)
4	(*S*)-(*R*)-BPPFOAc	12	65	2(*S*)
5	(*S*)-(*R*)-PPFA	12	42	31(*R*)
6	(*R*)-MOP(O-*i*-Pr)	12	90	9(*R*)
7[b]	(*R*)-BINAP(mono oxide)	24	60	16(*S*)

a: Unless otherwise stated, reactions were carried out by using 10 mol% $Pd_2(dba)_3$, 20 mol% ligand, 5 equiv K_2CO_3, 40 °C. b: 20 mol% $Pd(OAc)_2$, 20 mol% ligand were used.

of the resulting *exo*-olefin, in 35% overall yield. The absolute configuration of **3a** was determined as (*R*) by comparison of the optical rotation with published data. The absolute configuration of coupling product **3b** was determined using the HPLC analysis of compound **14**. Ozonolysis of the *exo*-olefin functionality of 4-nitrobenzonate **11**, in methanol at 0°C for 2 h, gave dialkyl ketone **14** in 30% yield. In contrast, optically active α,α′-disubstituted β-keto ester **15**,[11] obtained from the Michael addition of chiral β-enamino esters to ethyl acrylate, was converted to **14** in 59% yield. This was achieved by the protection of the ketone, reduction with LAH, mononitrobenzoylation and then deprotection. The absolute configuration of **3b** was determined by comparison of HPLC analysis with **14**. Therefore, the absolute configuration of the coupling product **3b** was determined as the (*R*)-form.



Scheme 3. (a) (1) TsCl, py, (2) $Et_2CuLi \cdot LiBr$, 2 steps 55%. (b) O_3, Me_2S, 60%. (c) (1) Bu_4NF/THF, (2) PNBCl, Et_3N, 2 steps 90%. (d) O_3, Me_2S, 36%. (e) (1) KHMDS, TBDMSCl, −78°C, (2) $LiAlH_4/Et_2O$, 0°C, (3) PNBCl, Et_3N, (4) Bu_4NF, AcOH, 4 steps 46%

In conclusion, we have succeeded in carring out the first example of an intramolecular asymmetric Suzuki–Miyaura reaction, leading to cyclopentane derivatives either with a tertiary or quaternary carbon center. Although enantiomeric excesses of products are still low to moderate, we believe that the present results will pave the way for further progress.

Acknowledgements

We thank Prof. A. Togni, for giving us an arsine compound (PAsFA). We also thank Dr. M. Sawamura for giving us a *trans*-chelating chiral diphosphine ligand (*R,R*)-(*S,S*)-TRAP.

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