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Abstract

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Keywords

CMMB

Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

SYNTHESIS OF CHIRAL ALLYLIC AMINES VIA PALLADIUM(0) CATALYSED ALLYLATIONS OF ALLYLIC CARBONATES WITH CHIRAL SULFINAMIDE ANIONS

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The palladium(0) catalysed allylation reactions of allylic carbonates with chiral sulfinamide anions to give unstable allylic sulfinamide products are described. These products are readily converted to stable, chiral *N*-benzoyl or *N*-tosyl allylic amine derivatives with poor to modest enantiomeric purities (ee 23-41%).

Key words: allylic sulfoximines; allylic sulfinamides; allylic carbonates; allylic amines; chiral amines; allylation; palladium(0) catalysed reactions.

INTRODUCTION

Chiral amines are important compounds in organic chemistry. They have been employed as chiral bases,[1a] nucleophiles,[1b] auxiliaries,[1c] and ligands[1d] for asymmetric synthesis. In particular, allylic amines are useful compounds for organic synthesis[2] and have featured as key structural components of peptide isosteres.[3] We recently reported the synthesis of chiral *N*-tosyl allylic amines **5** via the palladium(0) catalysed rearrangement reactions of chiral allylic sulfoximines **1** to chiral allylic sulfinamides **4** (Scheme 1).[4-11] These rearrangements occur via

the intermediate (η^3-allyl)palladium(II) species **2** in which the ambident nucleophilic sulfinamide counteranion **3** attacks the palladium complex as a nitrogen nucleophile to give the rearranged allylic sulfinamide products **4**. Mild methanolysis of the S-N bond in **4**, by treatment with methanol and triethylamine at RT, then gives the chiral *N*-tosyl allylic amine products **5**.
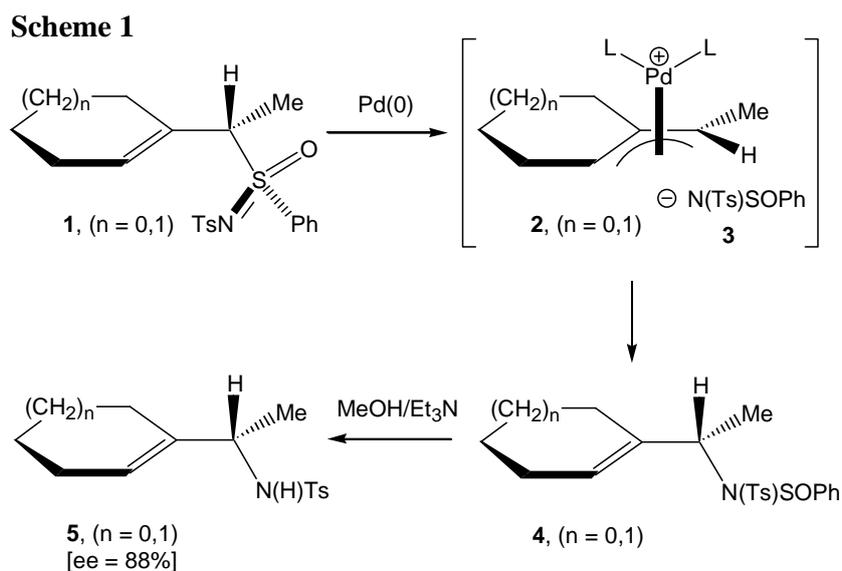
Scheme 1

In principle, chiral allylic sulfinamides can also be prepared from the reaction of achiral (η^3-allyl)palladium(II) cationic species (e.g. **8** in Scheme 2), that are generated from their corresponding racemic allylic acetates or carbonates[12] (e.g. **7** in Scheme 2), with a chiral sulfinamide anion (e.g. **9** in Scheme 2). In this paper we describe our attempts to prepare chiral allylic amines from the palladium(0) catalysed reactions of racemic allylic carbonates with optically active sulfinamides.

Scheme 2 (* denotes stereogenic centre)
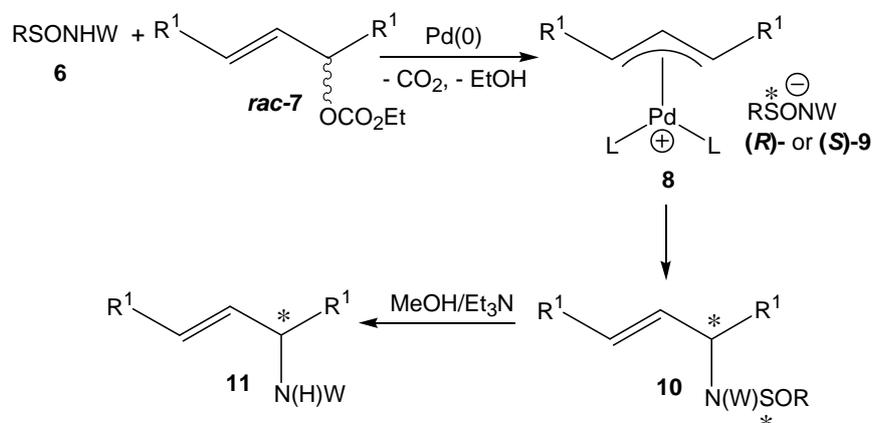
RESULTS AND DISCUSSION

The know chiral sulfinamides, (*R*)-**12**, (*S*)-**12** and (*S*)-**13**, were prepared by the methods of Davis[13] and Ellman[14] or purchased from the Aldrich Chemical Company. These compounds were used to prepare the *N*-benzoyl and *N-tert*-butoxycarbonyl (NBoc) derivatives, (*R*)-**14**, and (*S*)-**15** respectively, in good yields (83-85%) according to Scheme 3. These derivatives were best prepared using potassium hydride as the base and the acid anhydride ((PhCO)$_2$O or Boc$_2$O) as the acylating agent.[15]

(*R*)-**12**   (*S*)-**12**   (*S*)-**13**

Scheme 3

(*R*)-**14**   (*S*)-**15**
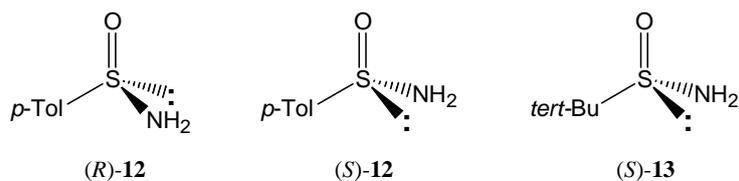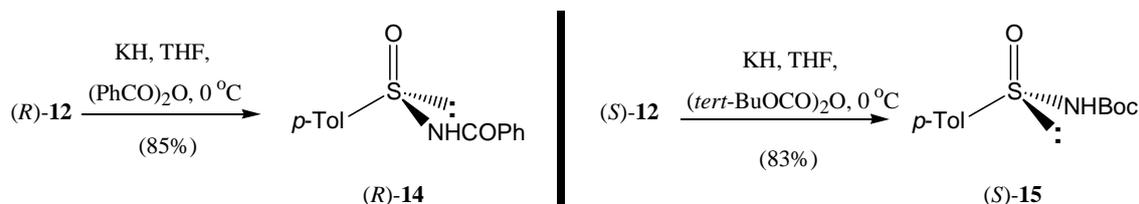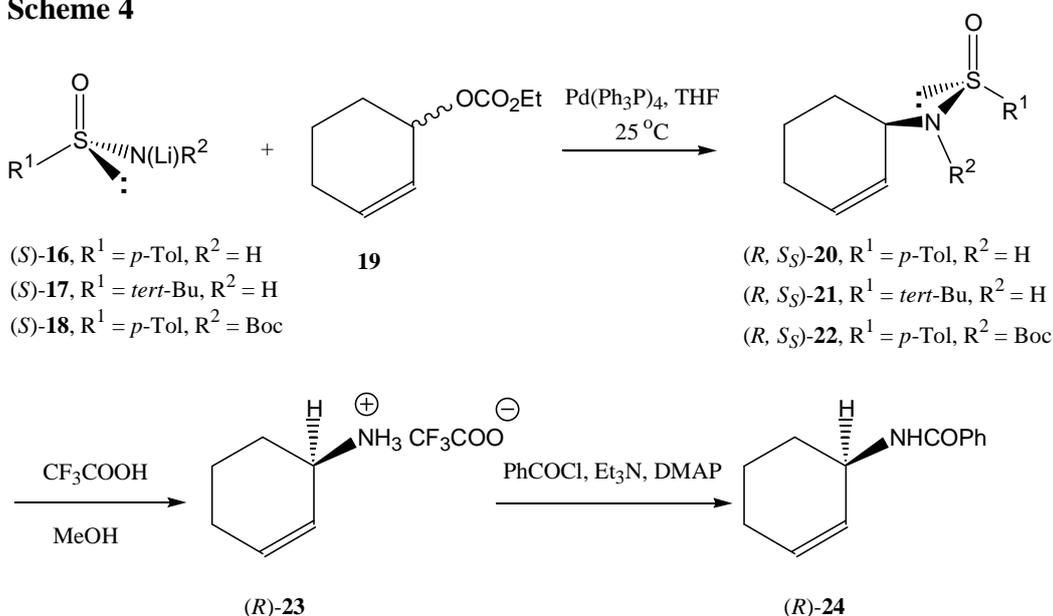
Treatment of a solution of the racemic allylic carbonate **19** in THF with 5 mol% tetrakis(triphenylphosphine)palladium(0) [Pd(PPh$_3$)$_4$] in the presence of the lithium salts **16, 17**

and **18**, (prepared from their respective sulfinamides, (*S*)-**12**, (*S*)-**13** and (*S*)-**15**) gave the unstable allylic sulfinimdes **20**, **21** and **22**, respectively (Scheme 4).[16] The crude products were immediately treated with trifluoroacetic acid / MeOH[17] to give the salt **23** which was converted to the known (*R*)-benzamide **24** upon treatment with benzoyl chloride and triethylamine (Scheme 4). Purification of **24** by column chromatography gave pure samples of this compound in poor overall yields (17-24% for the 3 chemical steps, Table 1). The (*R*)-configuration of **24** was evident from the sign of its specific rotation and the enantiomeric purity of these samples were estimated from the magnitude of their specific rotations when compared to the literature value for (*R*)-**24**.[18]

Scheme 4

(*S*)-**16**, R^1 = *p*-Tol, R^2 = H
(*S*)-**17**, R^1 = *tert*-Bu, R^2 = H
(*S*)-**18**, R^1 = *p*-Tol, R^2 = Boc

19

(*R, S$_S$*)-**20**, R^1 = *p*-Tol, R^2 = H
(*R, S$_S$*)-**21**, R^1 = *tert*-Bu, R^2 = H
(*R, S$_S$*)-**22**, R^1 = *p*-Tol, R^2 = Boc

(*R*)-**23**

(*R*)-**24**

A better overall yield of **24** was obtained from the palladium(0) catalysed reaction of racemic **19** with the lithium salt **25** (Scheme 5). Mild methanolysis of the unstable product **26** (Scheme 5), followed by purification by column chromatography, gave (*S*)-**24** in 57% overall yield (Table 1). The enantiomeric purities of **24** (Table 1) obtained from the reactions of lithiated, *N*-unsubstituted sulfinamides, **16** and **17**, were poor (23-24%) while the lithiated, *N*-acylated sulfinamides, **18** and **25**, gave **24** in better, but still modest, enantiomeric purities (41%). The poor overall yields in the case of **16**-**18** may be a consequence of the sulfinamide anion
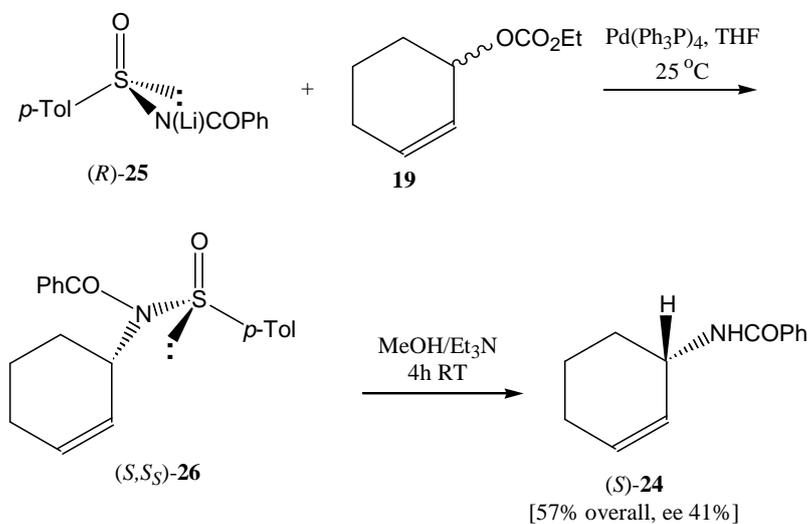
acting as a base rather than as a nucleophile on the intermediate (η^3-allyl)palladium(II) cationic species (**28** in Scheme 6).

Table 1. Synthesis of (*R*)- and (*S*)-**24** from **19**

N-lithiated sulfoximine	Overall yield (%) of **24** from **19**	$[\alpha]_D^{24}$ (CHCl₃) of **24**	Ee (%) of **24**[a]
(*S*)-**16**	17	43	24
(*S*)-**17**	18	41	23
(S)-**18**	24	72	41
(*R*)-**25**	57	-72	41

[a] Based upon $[\alpha]_D$ 157.9° (CHCl₃) for (*R*)-**24** of 90% ee.[18]

Scheme 5

The anion **25** would be expected to have a structure similar to a lithiated sulfoxide,[19] with chelation between the lithium cation and the N and O groups of the anion as shown in structure **27** (Scheme 6). The bulky *p*-Tolyl and COPh groups would be expected to have a *trans*-relationship. Electrophilic attack on **27** would be expected to occur on the same face as the lithium cation.[19] The stereochemical outcome of the reaction involving **25** and **19** can be

rationalized as arising from attack of the lithium chelated anion **27** on the (η^3-allyl)palladium(II) cationic species **28** shown in Scheme 6. In this orientation steric interactions between the bulky *p*-Tolyl group on the anion and the cyclohexenyl ring are minimized.

Scheme 6
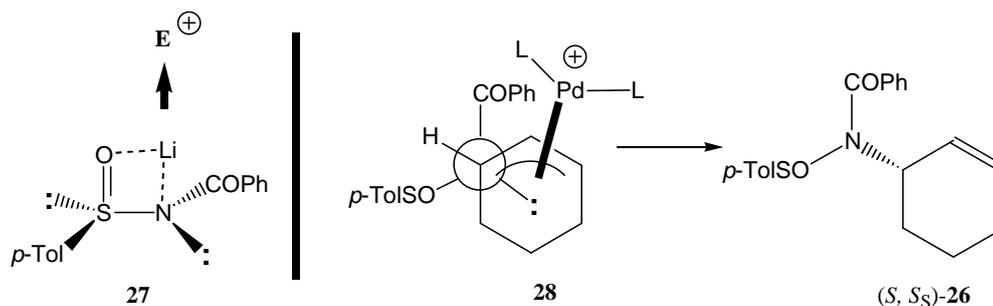
The palladium catalysed reaction of racemic **29** and lithiated sulfinamide (*S*)-**16**, followed by hydrolysis of the resulting sulfinamide and then tosylation, gave the known sulfonamide (*S*)-**30**[20] in poor overall yield and enantiomeric excess (Scheme 7).

Scheme 7
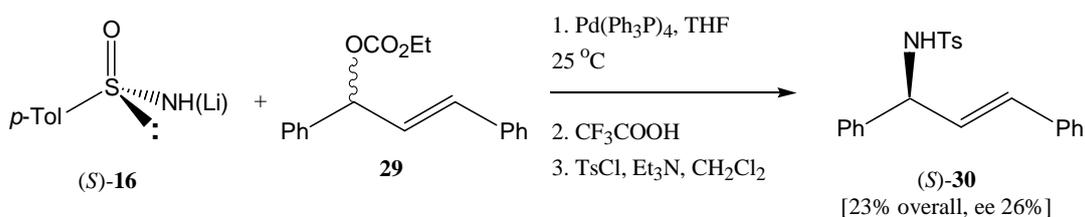
In conclusion, we have demonstrated that chiral *N*-protected allylic amines can be prepared via the palladium(0) catalysed allylation reactions of allylic carbonates with chiral sulfinamide anions. The enantiomeric purities of these derivatives, however is poor to modest (ee 23-41%). Other methods that use of chiral ligands for palladium(0) give such products in much higher enantiomeric purities.[12]

EXPERIMENTAL

ALLYLIC SULFINAMIDES

General methods were as described previously,[6] all NMR spectra were recorded in CDCl$_3$ solution at 300 MHz (^{1}H NMR) or 75.6 MHz (^{13}C NMR). The following abbreviations have been used DCM (dichloromethane), TFA (trifluoroacetic acid), THF (tetrahydrofuran) , LHMDS (lithium hexamethyldisilazane) and RT (room temperature).

(R)-N-Benzoyl- 4-methylbenzenesulfinate [(*R*)-**14**]

To a suspension of KH (35% in oil, 4.3 g, 37.7 mmol) in dry THF (62 mL) at 0 $^{\text{O}}$C under a nitrogen atmosphere was added (*R*)-p-toluenesulfinamide (1.95 g, 12.6 mmol) in several portions. A solution of benzoic anhydride (3.02 g, 13.4 mmol) in THF (25 mL) was then added dropwise over a period of 35 min. The mixture was then added dropwise to an aqueous solution of K$_2$CO$_3$ (13 mL, 1 M) to quench the remaining KH. The mixture was concentrated *in vacuuo*, acidified to pH 8-9 with 1 M HCl, and extracted with DCM (3 x 30 mL). The organic layers were combined and washed with a saturated solution of NaHCO$_3$ (3 x 30 mL), dried (MgSO$_4$) and evaporated. The crude product was purified by recrystallization from EtOAc/hexane to give **14** as a white solid (2.77 g, 85%), mp 81-83 $^{\text{O}}$C. ^{1}H NMR: δ 7.84-7.81 (2H, m), 7.60-7.50 (3H, m), 7.44-7.39 (2H, m), 7.31-7.27 (2H, m), 2.45 (3H, s); ^{13}C NMR: δ 167.5, 142.4, 140.4, 133.0, 131.5, 129.9, 128.6, 128.0, 124.9, 21.4; $[\alpha]_D^{24}$ -117.6 (c = 0.074, in CHCl$_3$); MS (CI + ve): *m/z* 260 (M + H$^+$, 50%), 139 (100), 122 (80); HRMS: Calcd for: C$_{14}$H$_{13}$NO$_2$S = 259.06668; Found: 259.06676.

(S)-N-tert-butyloxycarbonyl- 4-methylbenzenesulfinate [(*S*)-**15**]

The titled compound was prepared by the method described above for the synthesis of **14** except that (*S*)-p-toluenesulfinamide and di-*tert*-butyldicarbonate were used instead of the (*R*)-p-toluenesulfinamide and benzoic anhydride, respectively. Recrystallization of the crude reaction product from EtOAc/hexane gave **15** as a white solid (2.1g, 83%), mp 98-101$^{\text{O}}$C. ^{1}H NMR: δ 7.63-7.57 (2H, m), 7.34-7.28 (2H, m), 4.42 (1H, br), 2.43 (3H, s), 1.52 (9H, s); ^{13}C NMR: δ 152.6, 141.9, 140.2, 129.6, 124.6, 83.0, 27.8, 21.2; $[\alpha]_D^{24}$ 81.0 (c = 0.1, in CHCl$_3$); MS (CI + ve): *m/z* 256 (M + H$^+$, 10%), 200 (100), 156 (50);. HRMS: Calcd for: C$_{12}$H$_{17}$NO$_3$SNa = 278.08268; Found: 278.0825 (M + Na$^+$).

(R)-N-Cyclohex-2-enyl-benzamide (**24**)

A general procedure: A solution of (*S*)-*p*-toluenesulfinamide (310 mg, 2 mmol) in dry THF (12 mL) at –78 ^{O}C under a nitrogen atmosphere was treated dropwise with LiHMDS (2 mmol, 2 mL, 1.0 M in THF) and the solution was stirred for 30 min. The mixture was then treated with a solution of the allylic acetate **19** (374 mg, 2.2 mmol) and Pd(PPh$_3$)$_4$ (116 mg, 5 mol%) in THF (10 mL) at –78 ^{O}C. The reaction was warmed to 25-30°C and stirred for 40 h. The THF was then removed using a vacuum rotatory evaporator. The crude reaction mixture was treated with TFA (0.78 mL, 10 mmol) and MeOH (10 mL) at 0 ^{O}C. The reaction was warmed to RT and stirred for 4 h. The volatiles were removed, and the crude reaction mixture was treated with Et$_3$N (6 mL, 8.4 mmol), PhCOCl (340 mg, 0.28 mL, 2.4 mmol) and a few crystals of DMAP in dry DCM (20 mL) at 0 ^{O}C. The mixture was stirred at RT overnight. The reaction mixture was diluted with DCM (50 mL) and washed with water (2 x 20 mL) and then dried (MgSO$_4$). The DCM was evaporated and the crude product was purified by column chromatography on silica gel. Elution with 2-15% ethyl acetate/hexane gave **24** (67 mg, 17%), $[\alpha]_D^{24}$ 42.7^o (c = 0.06, in CHCl$_3$), 24%ee, (Lit.[18] $[\alpha]_D$ 157.9^o (c = 6.0 in CHCl$_3$) for **24** of 90%ee with the *R* configuration). ^{1}H NMR: δ 7.79-7.76 (2H, m), 7.52-7.39 (3H, m), 6.19-6.17 (1H, br), 5.94-5.88 (1H, m), 5.71-5.66 (1H, m), 4.73-4.67(1H, m), 2.09-1.95 (3H, m), 1.73-1.60 (3H, m); ^{13}C NMR: δ 166.7, 134.7, 131.3, 131.2, 128.5, 127.5, 126.8, 45.0, 29.4, 24.8, 19.7; MS (CI + ve): *m/z* 202 (M + H$^+$, 70%), 105 (100).

(S)-N-Cyclohex-2-eny- benzamide (**24**)

A solution of (*R*)-*N*-benzoyl-p-toluenesulfinamide **14** (257 mg, 1 mmol) in dry THF (10 mL) at –78 ^{O}C under a nitrogen atmosphere was treated dropwise with LiHMDS (1.1 mmol, 1.1 mL, 1.0 M in THF) and the solution was stirred for 30 min. The mixture was then treated with a solution of the allylic acetate **19** (187 mg, 1.1 mmol) and Pd(PPh$_3$)$_4$ (58 mg, 5 mol%) in THF (10 mL) at –78 ^{O}C. The reaction mixture was warmed to 25 ^{O}C and was stirred for 48 h. The THF was then removed using a vacuum rotatory evaporator. The crude reaction mixture was dissolved in methanol (10 mL) and was treated with Et$_3$N (10 drops) and the solution was stirred at RT

overnight. The methanol was then evaporated and the crude product was dissolved in DCM (20 mL). The solution was washed with water (2 x 20 mL) and then dried (MgSO$_4$). The DCM was evaporated and the crude product was purified by column chromatography on silica gel. Elution with 2-15% ethyl acetate/hexane gave **24** (115 mg, 57.2%), $[\alpha]_D^{24}$ -72.4º (c = 0.014 in CHCl$_3$), 41%ee, (Lit.[18] $[\alpha]_D$ 157.9º (c = 6.0 in CHCl$_3$) for **24** of 90%ee with the *R* configuration).

(E)-N-(1,3-Diphenylprop-2-en-1-yl)4-methylbenzenesulfonamide (**30**)

To a solution of (*R*)-*p*-toluenesulfinamide (155 mg, 1 mmol) in dry THF (6 mL) at –78 ºC was added dropwise LiHMDS (1 mmol, 1 mL, 1.0 M in THF) and the mixture was stirred for 30 min. The mixture was then treated with a solution of allylic acetate **19** (264 mg, 1.1 mmol) and Pd(PPh$_3$)$_4$ (58 mg, 5 mol%) in THF (5 mL) at –78 ºC. The reaction mixture was warmed to room temperature and stirred for 18 h. The THF was then removed using a vacuum rotatory evaporator. The crude reaction mixture was treated with TFA (0.39 mL, 5 mmol) and MeOH (10 mL) at 0 ºC then at RT for 4 h. The volatiles were removed and the crude reaction mixture was dissolved in DCM (10 mL) and cooled to 0 ^{0}C and treated with Et$_3$N (3 mL, 4.2 mmol), *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) and a few crystals of 4-dimethylaminopyridine. The reaction was warmed to RT and stirred overnight. The mixture was diluted with DCM (20 mL) and washed with water (2 x 20 mL) and then dried (MgSO$_4$) and filtered. The DCM was evaporated and the crude product was purified by column chromatography on silica gel. Elution with 5-25% ethyl acetate/hexane gave **30** (84 mg, 23%), $[\alpha]_D^{24}$ 8º (c = 0.04 in CHCl$_3$), 26% ee, (Lit.[20] $[\alpha]_D$ -31º (c = 1.0 in CHCl$_3$) for **30** of 90% ee with the *R* configuration). ^{1}H NMR: δ 7.67-7-64 (2H, m), 7.28-7.24 (5H, m), 7.21-7.10 (7H, m), 6.35 (1H, d, J = 15.9 Hz), 6.07 (1H, dd, J = 15.9, 6.9 Hz), 5.11 (1H, dd, J = 6.9, 6.6 Hz), 5.00 (1H, d, J = 6.6 Hz), 2.33 (3H, s); ^{13}C NMR: δ 143.2, 139.6, 137.7, 136.0, 132.1, 129.4, 128.7, 128.4, 128.1, 127.9, 127.8, 127.3, 127.0, 126.5, 59.7, 21.4.

ACKNOWLEDGMENT

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