Notes

Palladium(0)-Catalyzed Reactions of Allylic Benzotriazoles with Enamines: A Novel Method for the Stereoselective Synthesis of (4*E*)-γ,δ-Unsaturated Ketones

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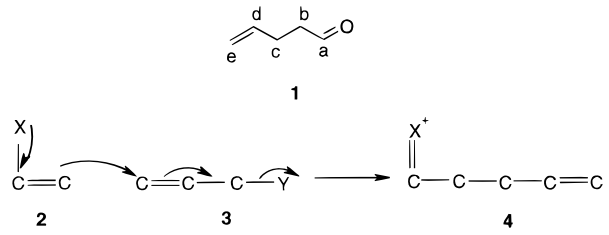
Introduction

γ,δ-Unsaturated ketones are common moieties in natural products.[1a−c] Possible synthetic approaches include those which form (i) the C(a)−C(b) bond (cf. Scheme 1) either by the reaction of allyl iodide and tosylmethyl isocyanide followed by hydrolysis[2] or by reacting *S* phenyl thioesters or Weinreb-type amides with homoallyl Grignard reagents,[3a,b] (ii) the C(c)−C(d) bond by conjugate addition of either lithium vinylcuprate or alkenyl-9-BBN to α,β-unsaturated carbonyl compounds,[4a,b] or (iii) the C(d)−C(e) bond by either the reaction of γ-keto aldehydes with Wittig reagents[5a,b] or anionic oxy-Claisen rearrangement of enolates of α-allyloxy ketones.[6] However, most common preparations of γ,δ-unsaturated ketones are by the formation of the C(b)−C(c) bond (Scheme 1). Such reactions usually involve a nucleophile of type **2** and an electrophile of type **3** as also shown in Scheme 1. Thus, Saucy et al. report that the reaction of isopropenyl ether (cf. **2**, X = OEt) with tertiary vinyl carbinols (cf. **3**, X = OH) under acid catalysis gives a mixture of (4*E*)- and (4*Z*)-γ,δ-unsaturated ketones in good yields.[7] Mukaiyama et al. prepare γ,δ-unsaturated ketones by reactions of secondary and tertiary allyl methyl ethers (cf. **3**, Y = OMe) with silyl enol ethers (cf. **2**, X = $OSiR_3$) in the presence of a catalytic amount of trityl perchlorate.[8] Under Lewis acid catalysis, silyl enol ethers react with some allylic halides or acetates to afford good yields of γ,δ-unsaturated ketones.[9] (α-Sulfenylmethyl)allyl acetates also react with silylated carbon nucleophiles to give γ,δ-unsaturated ketones in moderate to good yields.[10a,b]

Scheme 1



Palladium(0)-catalyzed nucleophilic substitution of allylic compounds is an important methodology in contemporary organic synthesis for the preparation of many classes of compounds.[11a−c] This method has also been used to prepare γ,δ-unsaturated ketones by forming the C(b)−C(c) bond (Scheme 1). Thus, under the catalysis of $Pd(OAc)_2/PPh_3$, piperidinocyclohexene reacts with allylic phenoxide to form 2-allylcyclohexanone, a γ,δ-unsaturated ketone, in moderate yield.[12] Palladium graphite can also be employed as a heterogeneous catalyst in the above reaction.[13] Utilizing $Pd(PPh_3)_4$ catalysis, allyl acetate or phenoxide reacts with various hexanone enamines to give 2-allylcyclohexanone in moderate yields.[14] Under neutral conditions, ketones and aldehydes react with 2-allylisourea in the presence of a catalytic amount of a palladium(0) complex to give γ,δ-unsaturated ketones and aldehydes.[15]

In recent years, benzotriazole has been widely used as a synthetic auxiliary.[16] Structurally diversified *N*-allylbenzotriazoles have been prepared very conveniently from allylbenzotriazole.[17] In a previous paper, we reported that, under the catalysis of palladium complex, *N*-allylbenzotriazoles can react readily with amines as a nitrogen nucleophile to give a wide range of allylamines in good yields.[18] Enamines are well-known carbon

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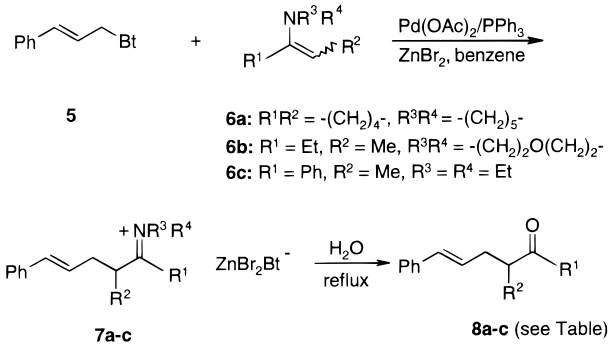
Table 1. Stereoselective Synthesis of (4*E*)-γ,δ-Unsaturated Ketones by Palladium-Catalyzed Reaction

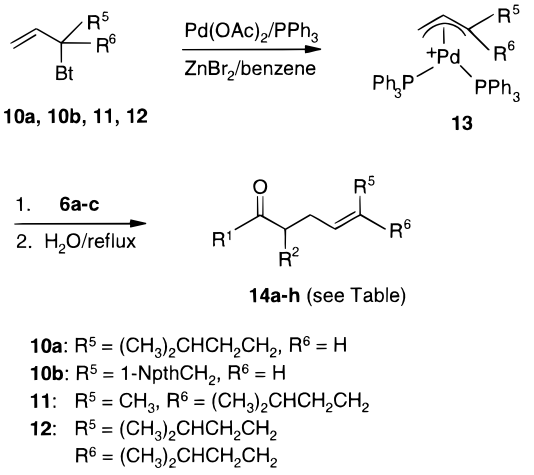
starting benzotriazole compd	product					
	no.	R^1	R^2	R^5	R^6	E/Z[a]
5	**8a**	$-(CH_2)_4-$				96/4
5	**8b**	CH_3CH_2	CH_3			98/2 (98/2)
5	**8c**	Ph	CH_3			95/5
10a	**14a**	$-(CH_2)_4-$		$(CH_3)_2CHCH_2CH_2$	H	99/1
10a	**14b**	CH_3CH_2	CH_3	$(CH_3)_2CHCH_2CH_2$	H	90/10 (94/6)
10b	**14c**	CH_3CH_2	CH_3	1-NpthCH$_2$	H	97/3
10b	**14d**	Ph	CH_3	1-NpthCH$_2$	H	96/4
10b	**14e**	$-(CH_2)_4-$		1-NpthCH$_2$	H	95/5
11	**14f**	CH_3CH_2	CH_3	CH_3	$(CH_3)_2CHCH_2CH_2$	90/10
12	**14g**	$-(CH_2)_4-$		$(CH_3)_2CHCH_2CH_2$	$(CH_3)_2CHCH_2CH_2$	99/1
12	**14h**	Ph	CH_3	$(CH_3)_2CHCH_2CH_2$	$(CH_3)_2CHCH_2CH_2$	98/2

[a] The E/Z ratios were determined by GC/MS on a Hewlett-Packard 5890 Series II Gas Chromatograph HP-5 (30 m × 0.32 mm × 0.25 μm) capillary column with the temperature range from 100 to 150 °C at the rate 10 °C/min. The E/Z ratio in parentheses are taken from the reaction using toluene as solvent.

Scheme 2



Scheme 3



nucleophiles in organic synthesis.[19] In this paper, we demonstrate that various allylic benzotriazoles react with enamines under palladium catalysis in the presence of stoichiometric zinc bromide to provide a general method for the synthesis of γ,δ-unsaturated ketones.

Results and Discussion

In the presence of $Pd(OAc)_2/PPh_3$ alone, 1-(γ-phenylallyl)benzotriazole **5** and enamine **6a** did not react in refluxing benzene. The departure of a benzotriazole anion as a leaving group is well-known to be facilitated in the presence of the Lewis acid $ZnBr_2$.[20a−c] Indeed, under the co-action of $Pd(OAc)_2/PPh_3$ and $ZnBr_2$, 1-(*E*)-phenylallylbenzotriazole **5** reacts smoothly with enamines **6a**−**c** to form iminium salts **7a**−**c**, which undergo subsequent hydrolysis to produce the expected γ,δ-unsaturated ketones **8a**−**c** in good yields (81−91%) (Scheme 2). Compound **8a** is a known compound synthesized via a stannyl enolate in 93% yield by Yasuda et al.[21] The (*E*)-configurations of products **8a**−**c** were determined by the vicinal coupling constants of the δ-proton signal of 16 Hz. Efficient reaction of **5** with enamine **6a** requires an excess of **6a** together with a catalytic amount of $Pd(OAc)_2/PPh_3$ and 2 equiv of $ZnBr_2$ (the reaction was much slower with 1.2 equiv of $ZnBr_2$). Enamine **6a** derived from a cyclic, **6b** from an acyclic, and **6c** from an aryl ketone can each act as the nucleophile to form a C−C bond by reaction with *N*-cinnamylbenzotriazole **5**. Qualitatively, the reaction rates are in the order **6a** > **6b** > **6c** for the three enamines.

α-Allylbenzotriazole (**9**) was lithiated by *n*-BuLi and treated subsequently with an alkyl halide to give regioselectively the α-monosubstituted allylbenzotriazoles **10a**,**b** in yields of 90−92% as previously reported.[17b] α-Allylbenzotriazole **9** can also be used in a double-lithiation technique with considerable flexibility: it was sequentially twice lithiated, and two of the same or different alkyl groups were introduced to give the α,α-disubstituted allylbenzotriazoles **11** and **12** (Scheme 3).

Catalysis by $Pd(OAc)_2/PPh_3$ and $ZnBr_2$ transforms α-substituted allylbenzotriazoles **10a**, **10b**, **11**, and **12** into cationic π-allylpalladium complex intermediates **13** (Scheme 3). The enamine **6** then attacks the γ-position of α-substituted allylbenzotriazoles **10a**, **10b**, **11**, and **12** which are sterically less hindered. No product from attack at the α-position of compounds **10a**, **10b**, **11**, and **12** was found. Both the monosubstituted **10a**,**b** and the disubstituted allylbenzotriazoles **11** and **12** produced the expected (*E*)-γ,δ-unsaturated ketones **14a**−**h** in yields of 80−90% after hydrolysis (Table 1). The (*E*)-configurations of products **14a**−**h** were demonstrated by the value of their vicinal coupling constants shown by the δ-proton signal to be 15.0−15.5 Hz.

The ratios of (*E*)-isomer to (*Z*)-isomer of **8a**−**c** and **14a**−**h** were obtained by GC/MS, in which there were two peaks possessing the same molecular weight. The

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analysis results show that this reaction has high stereoselectivities of (*E*)-γ,δ-unsaturated ketones ((*E*)-isomers >90%).

Conclusion

The structurally diversified allylic benzotriazoles **5**, **10a**, **10b**, **11**, and **12** react with various enamines smoothly under the action of $Pd(OAc)_2/PPh_3$ and $ZnBr_2$, affording a general method for the stereoselective synthesis of (4*E*)-γ,δ-unsaturated ketones **8a**−**c** and **14a**−**h**. Compared with previous methods, our method has the advantages of readily available starting materials, convenient manipulations, mild reaction conditions, high regio- and stereoselectivity, and good yields.

Experimental Section

General Comments. Melting points were determined on a hot stage apparatus without correction. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS and $CDCl_3$, respectively, as the internal reference. Compounds **5**, **10a**, **10b**, **11**, and **12** and enamines **6a**−**c** were prepared by the literature method.[17a−d]

General Procedure for the Synthesis of (4*E*)-γ,δ-Unsaturated Ketones 8a−c and 14a−i. Under argon, a mixture of allylbenzotriazole **5**, **10a**, **10b**, **11**, or **12** (2 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), PPh_3 (63 mg, 0.24 mmol), and $ZnBr_2$ (0.90 g, 4 mmol) was refluxed in benzene (10 mL) (toluene also was used as solvent in some cases; the reaction temperature was 80−90 °C) for 15 min. Then the solution of enamine **6** (4 mmol) in benzene (5 mL) (or toluene when toluene was used as solvent) was added, and the reaction mixture was refluxed for 1−3 h. After the evaporation of benzene, water (10 mL) was added and the mixture was refluxed for 30 min. NaOH (1 N, 30 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The organic phase was washed with a saturated solution of ammonium chloride (10 mL) and dried over magnesium sulfate. After removal of solvent, the residue was subjected to column chromatography to produce (4*E*)-γ,δ-unsaturated ketones **8a**−**c** and **14a**−**h**.

2-[(*E*)-3-Phenyl-2-propenyl]cyclohexanone (8a): oil; yield 91%; ^{1}H NMR δ 1.32−1.52 (m, 1H), 1.60−1.78 (m, 2H), 1.79−1.96 (m, 1H), 1.97−2.25 (m, 3H), 2.27−2.56 (m, 3H), 2.60−2.81 (m, 1H), 6.14−6.30 (m, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 7.14−7.62 (m, 5H); ^{13}C NMR δ 25.0, 27.9, 32.9, 33.5, 42.0, 50.6, 125.9, 126.9, 128.3, 128.4, 131.5, 137.5, 212.4. Anal. Calcd for $C_{15}H_{18}O$: C, 84.06; H, 8.48. Found: C, 83.63; H, 8.25.

(*E*)-4-Methyl-7-phenyl-6-hepten-3-one (8b): oil; Yield 90% (yield was 87% when toluene was used as solvent); ^{1}H NMR δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 2.17−2.31 (m, 1H), 2.37−2.59 (m, 3H), 2.60−2.72 (m, 1H), 6.05−6.19 (m, 1H), 6.38 (d, *J* = 15.7 Hz, 1H), 7.13−7.37 (m, 5H); ^{13}C NMR δ 7.6, 16.2, 34.4, 36.3, 45.9, 125.9, 127.0, 127.4, 128.4, 131.8, 137.2, 214.2. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.91; H, 9.06.

(*E*)-2-Methyl-1,5-diphenyl-4-penten-1-one (8c): oil; yield 81%; ^{1}H NMR δ 1.18−1.38 (m, 3H), 2.28−2.45 (m, 1H), 2.65−2.80 (m, 1H), 3.52−3.70 (m, 1H), 6.12−6.30 (m, 1H), 6.41 (d, *J* = 14.3 Hz, 1H), 7.12−7.40 (m, 5H), 7.40−7.60 (m, 3H), 7.95 (t, *J* = 3.9 Hz, 2H); ^{13}C NMR δ 17.2, 36.8, 40.9, 126.0, 127.0, 127.5, 128.2, 128.4, 128.6, 132.0, 132.9, 136.4, 137.3, 203.5. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.18; H, 7.24.

2-[(*E*)-6-Methyl-2-heptenyl]cyclohexanone (14a): oil; yield 90%; ^{1}H NMR δ 0.87 (d, *J* = 6.0 Hz, 6H), 1.18−1.28 (m, 2H), 1.28−1.45 (m, 1H), 1.45−1.60 (m, 1H), 1.60−1.80 (m, 2H), 1.80−2.20 (m, 6H), 2.20−2.50 (m, 4H), 5.30−5.50 (m, 2H); ^{13}C NMR δ 22.5, 24.8, 27.5, 27.9, 30.4, 32.5, 33.2, 38.7, 42.0, 50.8, 127.2, 132.6, 212.9. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.50; H, 11.51.

(*E*)-4,10-Dimethyl-6-undecen-3-one (14b): oil; yield 83%; (yield was 90% when toluene was used as solvent); ^{1}H NMR δ 0.86 (d, *J* = 6.6 Hz, 6H), 1.00−1.18 (m, 6H), 1.18−1.30 (m, 2H), 1.48−1.55 (m, 1H), 1.90−2.10 (m, 3H), 2.25−2.40 (m, 1H), 2.40−2.68 (m, 3H), 5.30 (dt, *J* = 15.3, 6.4 Hz, 1H), 5.42 (dt, *J* = 15.1, 6.4 Hz, 1H); ^{13}C NMR δ 7.6, 16.0, 22.4, 27.4, 30.3, 34.5, 36.2, 38.6, 46.2, 126.6, 133.1, 214.7. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.30; H, 12.81.

(*E*)-4-Methyl-8-(1-naphthyl)-6-octen-3-one (14c): oil; yield 82%; ^{1}H NMR δ 0.90−1.04 (m, 6H), 1.90−2.10 (m, 1H), 2.17−2.37 (m, 3H), 2.38−2.50 (m, 1H), 3.69 (d, *J* = 5.7 Hz, 2H), 5.41 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.74 (dt, *J* = 15.3, 6.3 Hz, 1H), 7.22−7.50 (m, 4H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 7.4, 16.0, 34.3, 35.8, 35.9, 45.7, 123.8, 125.3, 125.4, 125.5, 125.9, 126.7, 128.4, 128.8, 130.6, 131.7, 133.6, 136.4, 214.3. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.33. Found: C, 85.58; H, 8.53.

(*E*)-2-Methyl-6-(naphthyl)-1-phenyl-4-hexen-1-one (14d): oil; yield 82%; ^{1}H NMR δ 1.16 (d, *J* = 6.7 Hz, 3H), 2.11−2.25 (m, 1H), 2.45−2.60 (m, 1H), 3.41−3.58 (m, 1H), 3.74 (d, *J* = 5.8 Hz, 2H), 5.48 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.75 (dt, *J* = 15.2, 6.1 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.30−7.49 (m, 5H), 7.50−7.60 (m, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.80−8.02 (m, 4H); ^{13}C NMR δ 17.0, 36.0, 36.5, 40.7, 124.0, 125.4, 125.5, 125.7, 126.0, 126.8, 128.1, 128.2, 128.6, 128.9, 130.9, 131.9, 132.8, 133.7, 136.5, 136.6, 203.8. Anal. Calcd for $C_{23}H_{22}O$: C, 87.85; H, 7.07. Found: C, 87.87; H, 7.23.

2-[(*E*)-3-(1-Naphthalenyl)-2-propenyl]cyclohexanone (14e): mp 63.5−64.5 °C; Yield 86%; ^{1}H NMR δ 1.25−1.50 (m, 1H), 1.50−1.75 (m, 2H), 1.77−1.90 (m, 1H), 1.90−2.20 (m, 3H), 2.20−2.60 (m, 4H), 3.76 (d, *J* = 6.2 Hz, 2H), 5.50 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.72 (dt, *J* = 15.3, 6.3 Hz, 1H), 7.30−7.60 (m, 4H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 6.6 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 24.7, 27.8, 32.4, 33.2, 36.1, 41.9, 50.4, 124.0, 125.3, 125.5, 125.6, 125.9, 126.7, 128.5, 129.5, 130.2, 131.8, 133.7, 136.7, 212.5. Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.24; H, 7.97.

(*E*)-4,7,10-Trimethyl-6-undecene-3-one (14f): oil; yield 80%; ^{1}H NMR δ 0.79−0.98 (m, 6H), 0.99−1.18 (m, 6H), 1.18−1.37 (m, 2H), 1.40−1.58 (m, 1H), 1.59 (s, 3H), 1.92−2.04 (m, 2H), 2.04−2.18 (m, 1H), 2.23−2.40 (m, 1H), 2.41−2.52 (m, 2H), 2.53−2.64 (m, 1H), 5.04 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 7.5, 16.0, 22.4, 27.5, 29.6, 31.4, 34.4, 37.2, 37.4, 46.2, 120.9, 137.5, 214.7; HRMS (CI) *m*/*z* calcd for $C_{14}H_{26}O$ 210.1984, found 210.2056.

2-(3-Isopentyl-6-methyl-2-heptenyl)cyclohexanone (14g): oil; yield 87%; ^{1}H NMR δ 0.84−0.97 (m, 12H), 1.18−1.37 (m, 5H), 1.43−1.60 (m, 2H), 1.60−1.68 (m, 2H), 1.80−1.90 (m, 1H), 1.90−2.06 (m, 6H), 2.07−2.20 (m, 1H), 2.20−2.35 (m, 2H), 2.35−2.50 (m, 2H), 5.04 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR δ 22.5, 24.9, 27.2, 27.3, 27.7, 27.9, 28.2, 33.3, 34.8, 37.5, 37.6, 41.9, 51.2, 121.3, 141.7, 212.8; HRMS (CI) *m*/*z* calcd for $C_{19}H_{34}O$ 278.2610, found 278.2610.

5-Isopentyl-2,8-dimethyl-phenyl-4-nonen-1-one (14h): oil; yield 84%; ^{1}H NMR δ 0.83−1.02 (m, 12H), 1.15−1.35 (m, 7H), 1.40−1.60 (m, 2H), 1.90−2.10 (m, 4H), 2.10−2.30 (m, 1H), 2.40−2.55 (m, 1H), 3.40−3.60 (m, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 7.43−7.60 (m, 3H), 7.96 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 16.8, 22.5, 27.7, 28.0, 28.3, 31.8, 34.7, 37.4, 37.7, 41.2, 120.9, 128.2, 128.5, 132.7, 136.6, 142.4, 204.1. Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.87; H, 10.51.

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