

Tandem one pot asymmetric conjugate addition–vinyl triflate formation–cross coupling methodology

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Optically active vinyl triflates are obtained and employed in a series of one pot metal-catalyzed tandem asymmetric transformations.

The enantioselective conjugate addition of organometallic reagents to enones is one of the key methodologies for carbon–carbon bond formation.¹ In recent years, the discovery of monodentate phosphoramidites as chiral ligands for the copper catalyzed conjugate addition of dialkylzinc reagents,² has stimulated the development of numerous chiral ligands and catalysts for this asymmetric transformation.³

In a typical example of our asymmetric Cu-catalyzed 1,4-addition protocol, 2-cyclohexenone (**1**) reacts with a dialkylzinc reagent in the presence of a chiral copper catalyst, leading to an enantiomerically enriched zinc enolate **2** (Scheme 1). The chiral Cu-catalyst is frequently prepared *in situ* from a copper source (e.g. Cu(OTf)₂) and a chiral ligand (e.g. phosphoramidite **5**, Fig. 1). In the standard procedure, the intermediate zinc enolate **2** is converted during the acidic work up into the corresponding 3-substituted cyclohexanone **3**. The reactivity of this intermediate zinc enolate has been exploited in order to enhance the synthetic scope of the conjugate addition. Although the reactivity of a Zn enolate is lower than that of a Li, Na or Mg enolate,⁴ this methodology has allowed the development of tandem protocols to form additional C–C bonds, by trapping the enolate with electrophiles such as allyl⁵ and alkyl⁶ derivatives or aldehydes.^{2a,c}

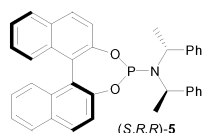
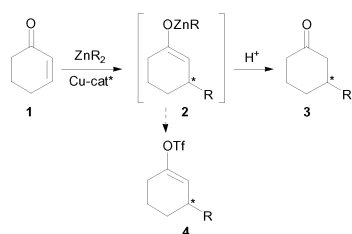


Fig. 1 Privileged monodentate phosphoramidite ligand.



Scheme 1 Cu-catalyzed asymmetric conjugate addition.

Recently, Alexakis and Knopff reported a tandem asymmetric conjugate addition–silylation of enantiomerically enriched zinc

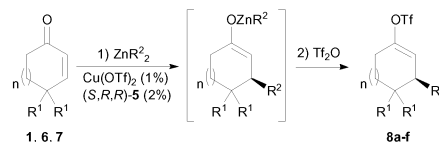
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enolates.⁷ The resulting silyl enol ethers were submitted to subsequent transformations to show their synthetic utility, such as in the formation of chiral vinyl triflates (**4**, Scheme 1). According to these authors,⁷ the transformation of the zinc enolate into the corresponding vinyl triflate could not be directly accomplished.

Bearing in mind the vast amount of palladium-catalyzed chemistry based on sp² carbon–triflate bonds,⁸ vinyl triflates are remarkably versatile synthons. Herein, we report a study demonstrating that enantiomerically enriched cyclic vinyl triflates can be obtained directly from cyclic enones in a tandem asymmetric conjugate addition–enolate trapping reaction. In addition, the synthetic utility of these chiral cyclic vinyl triflates is demonstrated.

Reaction of 2-cyclohexenone (**1**) with diethylzinc (1.15 eq.) in the presence of 1 mol% of Cu(OTf)₂ and 2 mol% of ligand (*S,R,R*)-**5** in toluene at –30 °C, led to the quantitative formation of the corresponding zinc enolate **2** (Scheme 2). Subsequent addition of triflic anhydride (Tf₂O, 2.2 eq.) to the reaction mixture at 0 °C, followed by aqueous work-up, afforded vinyl triflate **8a** in 83% yield and 97% ee (Table 1, entry 1).⁹ The application of these conditions to enones **6** and **7** also led the corresponding vinyl triflates in good yields and enantioselectivities ranging from 94–99% (entries 3 and 5). Employing dibutylzinc as the nucleophile we found lower yields of the vinyl triflates (55–58%) and a decrease in the enantioselectivity (entries 2, 4 and 6), compared to the use of diethylzinc. Remarkably, triflate **8d** was isolated in a modest 81% ee, while the enantioselectivity of the corresponding 3-substituted cyclohexanone **3**, resulting from the acidic quenching of the enolate, turned out to be 95% ee (entry 4). The different level of enantioselection seems to be the result of incomplete conversion in the conjugate addition step. Addition of triflic anhydride in the presence of the enone promoted an



Scheme 2 Synthesis of chiral vinyl triflates in one pot.

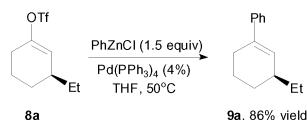
Table 1 Yields and ee's obtained for triflates **8a–f**^a

Entry	Enone	n	R ¹	R ²	Compound 8	Yield(%) ^b	Ee(%) ^c
1	1	1	H	Et	8a	83	97
2	1	1	H	Bu	8b	55	93
3	6	2	H	Et	8c	65	94
4	6	2	H	Bu	8d	55	81 (95) ^d
5	7	1	Me	Et	8e	74	99
6	7	1	Me	Bu	8f	58	95

^a See Scheme 2. ^b Isolated yields. ^c Determined by chiral GC. See ref. 10 for details. ^d Ee of the corresponding cyclohexanone **3** is given in brackets.

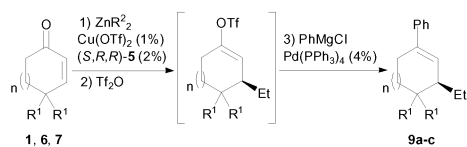
uncatalyzed 1,4-addition and therefore resulted in a decrease of the enantiomeric excess.

Optically active vinyl triflates are interesting building blocks, which can easily be transformed by palladium-catalyzed coupling reactions.⁸ Among those reactions, we decided to test the palladium-catalyzed coupling with organozinc reagents. Indeed, reaction of triflate **8a** with PhZnCl (1.5 eq.) in the presence of 4 mol% of Pd(PPh₃)₄ in THF at 50 °C afforded the chiral hydrocarbon **9a** in 86% yield (Scheme 3). Notably, chiral olefins are not only of fundamental interest but have recently been used as ligands in Rh-catalyzed asymmetric addition of arylboronic acids.¹¹

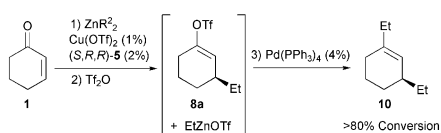


Scheme 3 Pd-catalyzed coupling reaction of vinyl triflate **8a**.

This result prompted us to develop a tandem version of this reaction, in which the Cu-catalyzed asymmetric conjugate addition, the formation of the vinyl triflate and its Pd-catalyzed coupling with an organometallic reagent were carried out in one pot. This procedure would avoid the isolation of vinyl triflates, directly transforming enones to enantiomerically enriched hydrocarbons. In our first attempts, a solution of PhZnCl and a catalytic amount of Pd(PPh₃)₄ were added to the reaction mixture obtained after the tandem Cu-catalyzed conjugate addition of Et₂Zn to cyclohexenone and subsequent enolate trapping reaction with Tf₂O. We were pleased to see the formation of olefin **9a**, although we also detected the formation of olefin **10** (Scheme 5). Apparently, there is competition in the Pd-catalyzed coupling reaction of the vinyl triflate between the *external* (PhZnCl) and the *internal* (EtZnOTf) organometallic reagents.¹² To avoid this side reaction we employed PhMgBr as an external organometallic reagent. As expected, the higher reactivity of the Grignard reagent allowed the isolation of the chiral olefin **9a** in good yield and high enantioselectivity (Scheme 4), in a one pot procedure from cyclohexenone over three consecutive steps (Table 2, entry 1).¹³ The use of other enones, **6** and **7**, also led to the formation of the corresponding chiral hydrocarbons **9b,c** in moderate to good yields (entries 2 and 3).¹⁴



Scheme 4 Synthesis of chiral olefins **9a–e** in one pot.



Scheme 5 Formation of chiral olefin **10** in one pot.

Table 2 Yields and ee's obtained for olefins **9a–c**^a

Entry	Enone	<i>n</i>	R ¹	Compound 9	Yield(%) ^b	ee(%) ^c
1	1	1	H	9a	46	96
2	6	2	H	9b	27	N.d. ^d
3	7	1	Me	9c	59	N.d. ^d

^a See Scheme 4. ^b Isolated yields. ^c Determined by chiral GC. See ref. 10 for details. ^d Not determined.

The Pd-catalyzed coupling between the vinyl triflate and RZnOTf, both formed *in situ* by the addition of Tf₂O to the zinc enolate, is by itself an interesting transformation. Preliminary results show that the addition of catalytic amounts of Pd(PPh₃)₄ to the reaction mixture, obtained from the first two steps shown in Scheme 5, lead to the formation of the chiral olefin **10** with more than 80% conversion.¹⁵ Therefore, the appropriate combination of two metal-catalyzed transformations (1,4-addition and cross-coupling) can lead to the transfer of both alkyl groups from the diorganozinc reagent to the enone.

In conclusion, cyclic enantiomerically enriched vinyl triflates can be easily obtained directly from cyclic enones in a tandem Cu-catalyzed asymmetric conjugate addition–enolate trapping reaction, without recourse to a separately isolated silyl ether as previously reported. In addition, these vinyl triflates can be used in Pd-catalyzed cross-coupling reactions with organometallic reagents to provide chiral olefins from enones in one pot, expanding the utility of the Cu-catalyzed asymmetric conjugate addition of dialkylzinc reagents.

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- 9 General procedure for the synthesis of vinyl triflates **8a–f** in one pot: In a Schlenk tube equipped with a septum and stirring bar, a mixture of Cu(OTf)₂ (3.6 mg, 0.01 mmol) and (*S,R,R*)-**5** (10.8 mg, 0.02 mmol) was dissolved in toluene (5 mL). After stirring under argon at room temperature for 30 min, the enone (**1**, **6** or **7**, 1 mmol) was added. The resulting mixture was cooled to –30 °C and the corresponding dialkylzinc reagent (solution in toluene, 1.15 mmol) was added dropwise. After stirring under argon for 2 h, Tf₂O (350 μL, 2 mmol) was added at 0 °C. The resulting mixture was allowed to reach room temperature overnight. Standard work-up with saturated aqueous NaHCO₃ and purification by column chromatography (SiO₂; pentane) afforded vinyl triflates **8a–f**. All the products gave satisfactory NMR (¹H, ¹³C) and HRMS. Selected data for **8a** (see ref. 7): ¹H-NMR (300 MHz, CDCl₃): δ = 5.63 (s, 1H), 2.30–2.22 (m, 2H), 2.16 (m, 1H), 1.85 (m, 1H), 1.73 (m, 1H), 1.63 (m, 1H), 1.43–1.29 (m, 2H), 1.17 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H) ppm. ¹³C-NMR (75.5 MHz, CDCl₃): δ = 149.4 (C), 122.6 (CH), 118.6 (q, *J* = 320 Hz, C), 36.6 (CH), 28.2 (CH₂), 27.7 (CH₂), 27.1 (CH₂),

- 21.4 (CH₂), 11.0 (CH₃) ppm. HRMS for C₉H₁₃F₃O₃S, cal: 258.0537, found: 258.0526.
- 10 Enantiomeric excesses were determined by capillary GC analysis with a Chiraldex G-TA column for **8a**, **8c-e** and **9a**; a Chiraldex B-TA column for **8b** or a Chiraldex B-PM column for **8f**. Absolute configurations were determined by comparison of the configuration of the corresponding cyclohexanones **3** with those reported (see ref. 2a).
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- 12 The internal organometallic reagent EtZnOTf is presumed to be formed in addition to the vinyl triflate from the reaction of the zinc enolate with Tf₂O.
- 13 General procedure for the synthesis of olefins **9a-c** in one pot: Following the procedure in ref. 9, the reaction mixture of the corresponding vinyl triflate **8** was sequentially treated with Pd(PPh₃)₄ (46.2 mg, 0.04 mmol) in THF (0.6 mL) and PhMgBr (3 M in Et₂O, 500 mL, 1.5 mmol) at -78 °C. The resulting mixture was allowed to reach room temperature overnight. Standard work-up with saturated aqueous NaHCO₃ and purification by column chromatography (SiO₂; pentane) afforded olefins **9a-c**. All the products gave satisfactory NMR (¹H, ¹³C) and MS. Selected data for **9a**: ¹H-NMR (300 MHz, CDCl₃): δ = 7.36 (d, *J* = 7.0 Hz, 2H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 5.98 (s, 1H), 2.37–2.34 (m, 2H), 2.11 (m, 1H), 1.91–1.77 (m, 2H), 1.61 (m, 1H), 1.49–1.29 (m, 2H), 1.21 (m, 1H), 0.94 (t, *J* = 7.7 Hz, 3H) ppm. ¹³C-NMR (50.3 MHz, CDCl₃): δ = 142.6 (C), 136.2 (C), 129.7 (CH), 128.2 (2 CH), 126.5 (CH), 125.0 (2 CH), 37.6 (CH), 29.2 (CH₂), 28.3 (CH₂), 27.7 (CH₂), 22.1 (CH₂), 11.6 (CH₃) ppm. MS (EI) *m/z* (%): 186 (15), 157 (100).
- 14 The ee of **9b** and **9c** could not be determined but are assumed to be the same as for the corresponding triflates **8c** and **8e**, respectively.
- 15 The volatility of this hydrocarbon has prevented the determination of an accurate isolated yield.