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Synthesis of new chiral *N*-heterocyclic carbenes from naturally occurring podophyllotoxin and their application to asymmetric allylic alkylation

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Abstract—Chiral *N*-heterocyclic carbenes (NHC) were synthesized from naturally occurring podophyllotoxin. Their coordination with $[(\eta^3\text{-allyl})Pd(Br)]_2$ afforded (NHC)Pd(allyl)Br complexes, whose structures were unambiguously established by X-ray single crystal analysis. These chiral NHC and NHC-Pd-allyl complexes were found to catalyze the substitution reaction of allylic compounds with high conversions and enantioselectivities (up to 87% ee).

1. Introduction

Over the past decade, *N*-heterocyclic carbenes (NHC) have emerged as one of the most important classes of compounds used as ancillary ligands for a number of late transition metal mediated catalytic reactions.[1] In general, it appears that catalytic reactions, which employ transition-metal complexes of tertiary phosphines, may also be catalyzed using complexes of NHC; many of the precatalysts studied to date exhibit excellent thermal stability and the need for excess NHC ligand is not required.[1–3] The high thermal stability and good catalytic activity of metal complexes are due to the strong σ-donor properties of NHC combined with poor π-acceptor ability. A range of very active NHC catalysts have been synthesized in recent years. The most prominent examples are the second and third generation Grubbs olefin metathesis catalysts[4] as well as several novel palladium C–C coupling catalysts for Suzuki–Miyaura, Kumada and Heck-type reactions.[5] Recently, the potential of NHC-based ligands for asymmetric catalytic chemistry was realized and a number of chiral NHC ligands giving high enantioselectivities were prepared.[3] These include NHC-oxazoline hybrid ligands for iridium-catalyzed intermolecular hydrogenation of aryl alkenes;[6] rhodium-catalyzed hydrosilylation of ketones,[7] and a di-NHC ligand for rhodium-catalyzed hydrosilylation of ketones.[8] Ruthenium-catalyzed asymmetric olefin metathesis has also been reported.[9]

Podophyllotoxin **1**, a natural antitumor drug and a starting material for the preparation of a class of antitumor agents such as etoposide (VP-16), has a rigid structure and steric hindrance, so it should be a suitable building block for the design of chiral ligands. Additionally, this chiron is inexpensive and readily available via extraction from *Podophyllum peltatum* or synthesis from simple compounds.[10] Recently, we synthesized three new palladium complexes of chiral NHC ligands from naturally occurring podophyllotoxin, and found that they could catalyze the intermolecular asymmetric allylic alkylation reaction. Herein we report the primary results of this work.

2. Results and discussion

As shown in Scheme 1, four imidazolium salts **3a–d** were designed, in which a chiral center of podophyllotoxin moiety was directly attached to the N-1 of an imidazole ring. **1** was converted to mesylate **2** with mesyl chloride in the presence of triethylamine. Treatment of **2** with the corresponding 1-substituted imidazoles in CH_3CN gave the corresponding imidazolium mesylate salts **3** in yields ranging from 62% to 86%. Imidazolium salts are common precursors to NHC ligands. To probe the coordination mode

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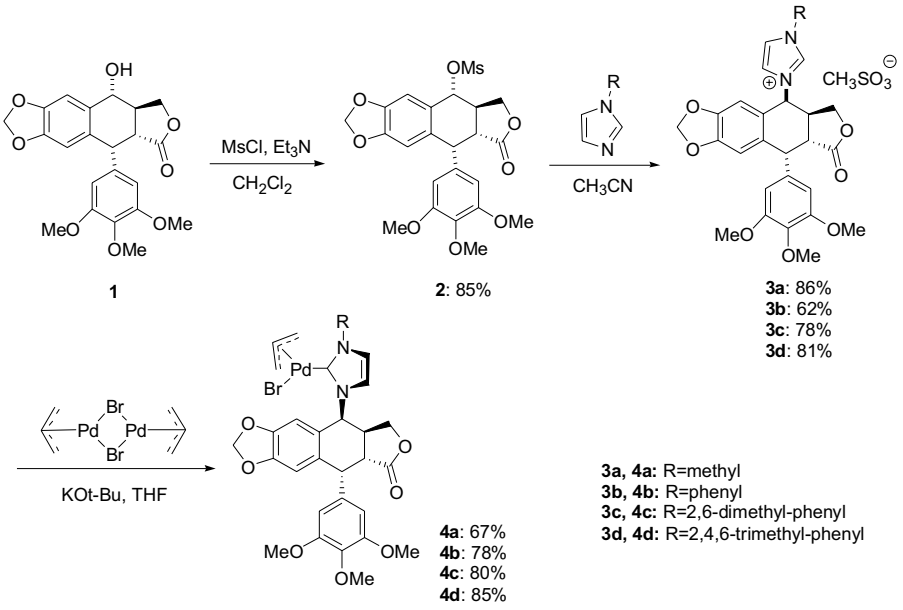


Scheme 1. Synthesis of chiral NHC precursors and their palladium complexes.

and conformations of these NHC ligands, (NHC)Pd-(allyl)Br complexes **4** were prepared via a reaction between imidazolium salts **3** and $[(\eta^3\text{-allyl})Pd(Br)]_2$ according to a published method.[11] The structure of complex **4a** was unambiguously established by X-ray single-crystal diffraction analysis (Fig. 1).[12]

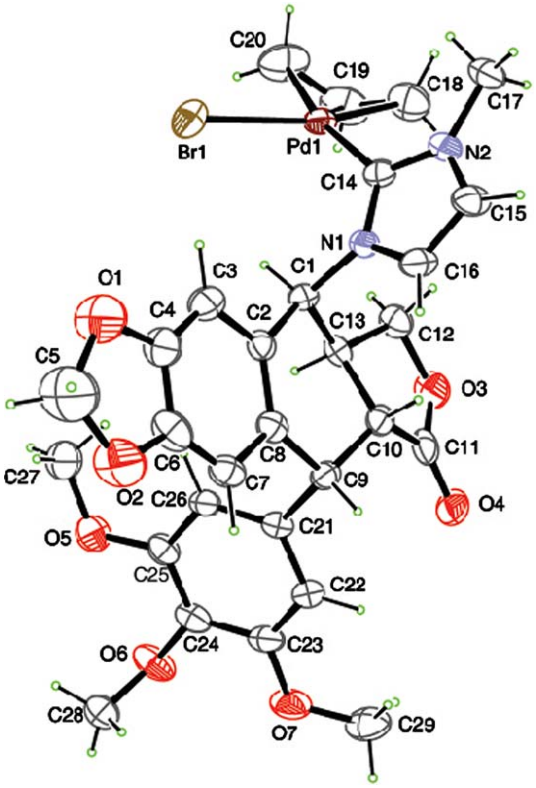
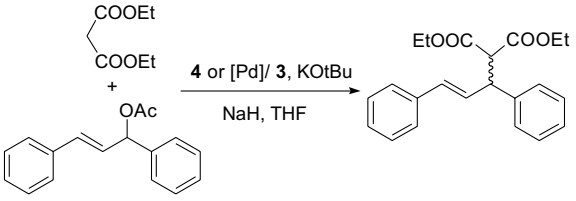


Figure 1. Molecular structure of complex **4a**. Selected bond lengths (Å): Pd(1)–C(14) = 2.048, Pd(1)–Br(1) = 2.500, Pd(1)–C(18) = 2.102, Pd(1)–C(19) = 2.134, Pd(1)–C(20) = 2.171.

Nolan et al. have demonstrated that mononuclear palladium-allyl complexes bearing achiral NHC ligands are efficient catalysts of several cross-coupling reactions.[11] Based on these results, we investigated the possibility of the chiral palladium-allyl complexes **4** as a catalyst in allylic alkylation reaction. The asymmetric allylic alkylation of (*E*)-1,3-diphenylprop-3-en-1-yl acetate with diethylmalonate was used as the model reaction and the results are summarized in Table 1.

Table 1. Asymmetric allylic alkylation catalyzed by **4** or [Pd]/**3**



Entry	Catalyst	Yield (%)[a]	[R] ee%[b]
1	**4a**	22	32
2	**4b**	82	53
3	**4c**	85	76
4	**4d**	83	79
5	**3a**/$Pd_2(dba)_3$/KOtBu	26	20
6	**3b**/$Pd_2(dba)_3$/KOtBu	68	54
7	**3c**/$Pd_2(dba)_3$/KOtBu	91	75
8[c]	**3c**/$Pd_2(dba)_3$/KOtBu	79	42
9	**3c**/$Pd(OAc)_2$/KOtBu	88	82
10	**3d**/$Pd(OAc)_2$/KOtBu	93	87

[a] Isolated yields.
[b] Determined by chiral HPLC (Pirkle (*R*,*R*)-whelk-O1).
[c] **3c**/$Pd_2(dba)_3$/KOtBu and *rac*-*E*-1,3-diphenyl allyl acetate were added together.

As shown in Table 1, either (NHC)Pd(allyl)Br complex **4a** (entry 1) or $Pd_2(dba)_3$ combining with NHC precursor **3a** (entry 5) gave poor yields and enantioselectivities, while complexes **4b**, **4c**, and **4d** bearing a bulky substituent at N-2 of imidazoline ring (entries 2–4) or $Pd_2(dba)_3$ combining with imidazolium salts **3b** and **3c** (entries 6 and 7) gave moderate to high yields and enantioselectivities. These results demonstrated that the catalytic activity and enantioselectivity strongly depend on the substituents at the N atom of imidazoline ring of ligands, which is similar to the published results.[11d,13] Replacement of the methyl at N-2 of the imidazoline moiety of **3a** or **4a** with phenyl (entries 2 and 6), 2,6-dimethylphenyl (entries 3 and 7) or 2,4,6-trimethylphenyl (entries 4 and 10) led to a dramatic improvement of yield and enantioselectivity. Additionally, $Pd(OAc)_2$ (entries 9 and 10) afforded a superior enantioselectivity as compared with $Pd_2(dba)_3$ (entry 6) when an in situ catalytic procedure was adopted.

3. Conclusion

We have prepared a new class of chiral NHC ligands and their palladium-allyl complexes from naturally occurring podophyllotoxin. Their application in a palladium-catalyzed allylic alkylation has been studied with high conversions (up to 93%) and enantioselectivities (up to 87% ee) being obtained.

4. Experimental

All reactions were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. DCM was dried with CaH_2 and THF was dried with sodium. All other solvents or reagents were used as supplied (analytical or HPLC grade) without prior purification.

The ^1H and ^{13}C NMR spectra were recorded on a Brucker Spectrospin Avance 500 or 400 spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Brucker Esruire 3000 Plus. HPLC measurements were performed with an Agilent 1100 instrument. Separations were carried out on Pirkle (R, R) Whelk-O1 analytical column (250 × 4.60 mm) with hexane/2-propyl alcohol as eluent.

4.1. General procedure for the synthesis of imidazolium salts 3

To a solution of podophyllotoxin **1** (2.07 g, 5 mmol) in DCM (40 mL) was added triethylamine (0.84 mL, 6 mmol) and mesyl chloride (0.48 mL, 6 mmol) at 0 °C. Then the mixture was stirred for 2 h at room temperature. After washing with water (2 × 20 mL) and brine (1 × 20 mL), the organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and crystallized from ethyl acetate/hexane to afford 2.1 g (85%) of **2**. Mesylate **2** (0.99 g, 2 mmol) and 1-substituted imidazole (6 mmol) were dissolved in CH_3CN (10 mL). The resulting solution was stirred at 80 °C for 24 h, and then cooled to room temperature. Most of the solvent was evaporated and ethyl acetate (50 mL) added. The resulting precipitation was collected by filtration and washed with ethyl acetate (2 × 50 mL) to give imidazolium mesylate salts **3** as an off-white powder.

Compound **3a**: 86% yield; ^1H NMR (500 MHz, D_2O): δ 3.14–3.15 (m, 1H), 3.27 (br, 1H), 3.54 (t, $J = 9.6$ Hz, 1H), 3.60 (s, 3H), 3.66 (s, 6H), 3.80 (s, 3H), 4.42 (t, $J = 7.6$ Hz, 1H), 4.58 (d, $J = 4.6$ Hz, 1H), 5.77 (s, 1H), 5.86 (s, 1H), 6.00 (d, $J = 3.3$ Hz, 1H), 6.25 (s, 1H), 6.33 (s, 2H), 6.72 (s, 1H), 7.39 (s, 1H), 7.47 (s, 1H), 8.52 (s, 1H); MS (ESI): $m/z = 479$ ($[M-MsO]^+$).

Compound **3b**: 62% yield; ^1H NMR (400 MHz, D_2O): δ 3.19–3.27 (m, 1H), 3.34–3.37 (m, 1H), 3.56 (s, 3H), 3.66 (s, 6H), 4.30 (d, $J = 8.4$ Hz, 1H), 4.51 (t, $J = 8.4$ Hz, 1H), 4.62–4.66 (m, 1H), 5.86 (s, 1H), 5.90 (s, 1H), 6.15 (d, $J = 4.8$ Hz, 1H), 6.34–6.41 (m, 2H), 6.45 (br, 1H), 6.81 (s, 1H), 7.49–7.62 (m, 5H), 7.79 (t, $J = 1.6$ Hz, 1H), 9.07 (s, 1H); MS (ESI): $m/z = 541$ ($[M-MsO]^+$).

Compound **3c**: 78% yield; ^1H NMR (400 MHz, D_2O): δ 1.82 (s, 3H), 1.90 (s, 3H), 3.02–3.07 (m, 1H), 3.25–3.29 (m, 1H), 3.39 (s, 3H), 3.56 (s, 6H), 4.40 (t, $J = 4.4$ Hz, 1H), 4.47–4.51 (m, 1H), 5.73 (s, 1H), 5.78 (s, 1H), 6.11 (br, 2H), 6.23–6.26 (m, 2H), 6.76 (s, 1H), 7.07–7.10 (m, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.55–7.58 (m, 1H), 7.65 (s, 1H); MS (ESI): $m/z = 569$ ($[M-MsO]^+$).

Compound **3d**: 81% yield; ^1H NMR (400 MHz, D_2O): δ 2.01 (s, 3H), 2.05 (s, 3H), 2.16 (br, 1H), 2.32 (s, 3H), 3.05–3.09 (m, 1H), 3.35–3.39 (m, 2H), 3.73 (s, 6H), 3.79 (s, 3H), 4.74 (br, 1H), 4.98 (br, 1H), 5.99 (s, 1H), 6.00 (s, 1H), 6.28 (s, 2H), 6.59 (s, 1H), 6.86 (br, 1H), 6.99 (s, 2H), 7.13–7.17 (m, 1H), 7.30–7.33 (m, 1H), 10.90 (br, 1H); MS (ESI): $m/z = 583$ ($[M-MsO]^+$).

4.2. General procedure for the synthesis of palladium-allyl complexes 4

A solution of **3** (0.3 mmol), $[Pd(\eta^3\text{-}C_3H_5)Br]_2$ (70 mg, 0.15 mmol) and potassium *tert*-butoxide (35 mg, 0.3 mmol) in THF (5 mL) was stirred for 5 h at room temperature under nitrogen. The mixture was filtered in air, and the precipitate washed with THF (2 × 10 mL). The filtrate was evaporated on a rotary evaporator and the residue purified by flash chromatography on silica gel with ethyl acetate/hexane (2:1) to give **4** as a white solid.

Compound **4a**: 67% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 2.76 (d, $J = 11.8$ Hz, 1H), 2.96–3.08 (m, 2H), 3.34–3.45 (m, 2H), 3.66 (d, $J = 5.0$ Hz, 1H), 3.78 (s, 6H), 3.81 (s, 3H), 3.88 (s, 3H), 4.10–4.14 (m, 1H), 4.22 (d, $J = 8.4$ Hz, 1H), 4.38 (d, $J = 7.2$ Hz, 1H), 4.72 (dd, $J = 5.0$ Hz, 12.6 Hz, 1H), 5.25–5.30 (m, 1H), 5.97 (s, 2H), 6.30 (d, $J = 16.1$ Hz, 2H), 6.52–6.58 (m, 2H), 6.95 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.2, 38.7, 41.7, 43.9, 52.1, 52.5, 56.5, 57.5, 57.9, 60.9, 68.2, 68.6, 73.0, 101.9, 108.3, 109.9, 110.2, 114.8, 115.5, 121.1, 122.7, 126.9, 132.6, 134.6, 148.2, 149.2, 153.0, 173.7, 181.5; MS (ESI): $m/z = 625$ ($[M-Br]^+$).

Compound **4b**: 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, $J = 12.4$ Hz, 1H), 2.94–3.00 (m, 2H), 3.02–3.13 (m, 2H), 3.32–3.37 (m, 1H), 3.70 (s, 6H), 3.74 (s, 3H), 4.14–4.18 (m, 2H), 4.36 (t, $J = 8.0$, 1H), 4.68 (d, $J = 5.0$ Hz, 1H), 5.00–5.10 (m, 1H), 5.90 (d, $J = 4.4$ Hz, 2H), 6.24 (s, 2H), 6.51 (s, 1H), 6.60 (d, $J = 1.6$ Hz, 1H), 6.78 (d, $J = 4.4$ Hz, 1H), 7.17–7.18 (m, 1H), 7.35–7.45 (m, 3H), 7.7 (s, 1H), 7.8 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.9, 40.4, 41.3, 43.7, 53.8, 56.1, 56.2, 57.5, 60.7, 66.3, 67.7, 71.1, 101.6, 107.8, 108.0, 110.1, 113.8, 118.2, 121.4, 124.8, 127.4, 129.1, 129.8, 130.4, 132.3, 134.4, 137.2, 147.2, 149.0, 152.4, 152.7, 173.4, 182.0; MS (ESI): $m/z = 687$ ($[M-Br]^+$).

Compound **4c**: 80% yield; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.57 (d, $J = 12.4$ Hz, 1H), 1.98 (s, 3H), 2.14–2.16 (m, 1H), 2.32 (s, 3H), 2.83–3.00 (m, 2H), 3.03–3.08 (m, 1H), 3.30–3.35 (m, 1H), 3.69 (s, 3H), 3.73 (s, 6H), 4.10 (dd, $J = 1.2$ Hz, 7.2 Hz, 1H), 4.17 (dd, $J = 7.6$ Hz, 8.4 Hz, 1H), 4.60–4.72 (m, 2H), 4.96–5.07 (m, 1H), 5.89–5.93 (m, 2H), 6.25 (s, 1H), 6.42 (s, 1H), 6.50–6.55 (m, 1H), 6.63 (d, $J = 1.6$ Hz, 1H), 6.91–6.93 (m, 1H), 7.06–7.13 (m, 2H), 7.17–7.23 (m, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 19.0, 36.9, 41.3, 43.6, 45.6, 53.0, 56.1, 56.2, 56.9, 60.5, 67.8, 69.8, 72.4, 101.2, 107.8, 108.0, 110.0, 114.2, 117.9, 121.0, 126.5, 127.6, 128.7, 129.3, 132.3, 134.3, 135.3, 136.5, 138.2, 147.9, 148.8, 152.6, 173.3, 182.6; MS (ESI): $m/z = 715$ ($[M-Br]^+$).

Compound **4d**: 85% yield; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.68 (d, $J = 12.4$ Hz, 1H), 1.99 (s, 3H), 2.13–2.16 (m, 1H), 2.31 (s, 3H), 2.33 (s, 3H), 2.91 (d, $J = 13.2$ Hz, 1H), 3.02 (dd, $J = 4.8$ Hz, 14.4 Hz, 1H), 3.08–3.12 (m, 1H), 3.35–3.45 (m, 2H), 3.75 (s, 6H), 3.79 (s, 3H), 4.16–4.18 (m, 1H), 4.22 (dd, $J = 7.2$ Hz, 8.8 Hz, 1H), 4.72 (d, $J = 5.2$ Hz, 1H), 5.02–5.12 (m, 1H), 5.97 (s, 2H), 6.30 (s, 1H), 6.47 (br, 1H), 6.56–6.60 (m, 1H), 6.66 (d, $J = 1.6$ Hz, 1H), 6.91–6.99 (m, 3H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 17.7, 21.0, 36.6, 41.4, 43.7, 56.3, 56.6, 58.5, 60.6, 68.1, 77.2, 102.0, 108.0, 109.0, 110.4, 122.2, 123.4, 123.8, 129.9, 130.0, 130.4, 133.7, 133.8, 133.9, 137.5, 139.4, 141.6, 148.3, 149.7, 152.8, 152.9, 172.9; MS (ESI): $m/z = 729$ ($[M-Br]^+$).

4.3. Typical procedures for asymmetric allylic alkylation

Method A: To a solution of *rac*-*E*-1,3-diphenyl allyl acetate (126 mg, 0.5 mmol) in THF (3 mL) was added **4** (0.025 mmol) under nitrogen. The mixture was stirred at room temperature for 15 min. Then a solution of diethylmalonate (240 mg, 1.5 mmol) and NaH (35 mg, 1.45 mmol) in THF (2 mL) was added and the reaction mixture heated to 50 °C for 15 h.

Method B: **3** (0.025 mmol), $Pd_2(dba)_3$ (11 mg, 0.0125 mmol) or $Pd(OAc)_2$ (6 mg, 0.025 mmol), and KOtBu (3 mg, 0.025 mmol) in THF (3 mL) were stirred at room temperature under nitrogen for 30 min, then *rac*-*E*-1,3-diphenyl allyl acetate (126 mg, 0.5 mmol) was added and stirred for 15 min. Then a solution of diethylmalonate (240 mg, 1.5 mmol) and NaH (35 mg, 1.45 mmol) in THF (2 mL) was added and the reaction mixture heated to 50 °C for 15 h. After cooling to room temperature, aqueous saturated NH_4Cl solution (10 mL) was added, and the reaction mixture extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel with ethyl acetate/hexane (1:30). After evaporation of the solvent under reduced pressure the pure product was obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, $J = 7.1$ Hz, 3H), 1.22 (t, $J = 7.1$ Hz, 3H), 3.92 (d, $J = 11.0$ Hz, 1H), 3.97 (dd, $J = 2.5$ Hz, 7.1 Hz, 2H), 4.17 (dd, $J = 2.5$ Hz, 7.1 Hz, 2H), 4.26 (dd, $J = 8.6$ Hz, 11.0 Hz, 1H), 6.32 (dd, $J = 8.6$ Hz, 15.8 Hz, 1H), 6.48 (d, $J = 15.8$ Hz, 1H), 7.19–7.31 (m, 10H); MS (ESI): $m/z = 375$ ($[M+Na]^+$).

Acknowledgments

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12. CCDC 296363 contains the supplementary crystallographic data for compound **4a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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