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Palladium asymmetric reduction of β-carboline imines mediated by chiral auxiliaries assisted by microwave irradiation

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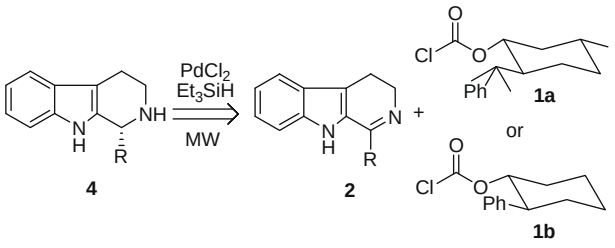
ABSTRACT

An alternative synthetic approach for the introduction of chirality in β-carboline moiety through in situ reduction of *N*-acyliminium ion intermediates generated from imine **2** and chloroformate of 8-phenylmenthyl as chiral auxiliary was achieved. The method applied microwave-assisted irradiation and used $PdCl_2/Et_3SiH$ protocol as a mild reducing agent, which decreased reaction times to minutes when compared to the conventional thermal reactions. The diastereoselectivity (4–12:1) of the reduction produced *R*-amines, which were assigned after chiral auxiliary removal and spectroscopic data compared to products obtained from Noyori asymmetric hydrogenation catalyst.

Despite great developments in synthetic organic chemistry, there are still few methodologies that allow the stereoselective construction of pre-determined moieties in some classes of compounds. In this context, particular attention in efficient synthetic routes for novel chemotypes is actively being pursued when stereoselectivity is required. Chiral auxiliaries based upon the cyclohexane frame have been explored in several asymmetric reactions. A large number of reaction types have been examined using chiral auxiliaries of this type, although those that have been explored with the readily available menthol rarely provide what would be considered practical levels of control. On the other hand, auxiliaries that bear phenyl substituents such as Corey's 8-phenylmenthol (**1a**) and Whitesell *trans*-2-phenylcyclohexanol (**1b**) have provided excellent levels of control (Scheme 1).[1] As part of our efforts in the field of biologically relevant β-carbolines, we turned our attention toward an alternative synthetic route for the preparation of chiral tetrahydro-β-carbolines such as **4**.[2]

Numerous methods for the synthesis of optically active amines are known, few being based on catalytic asymmetric synthesis. Among the most popular is the asymmetric hydrogenation of ketimines or enamides using chiral Rh(I), Ir(I), or Ru(II) complexes.[2] Thus, we investigated the scope of reduction of imines such as **2** mediated by chiral auxiliaries in a one-pot manner. The methodology is based on the use of chloroformates **1a**,**b** as chiral auxiliaries for the reduction of dihydro-β-carbolines.[3] Furthermore, the $PdCl_2/Et_3SiH$ protocol[3,4] was employed as palladium hydride source and the reactions were assisted by microwave irradiation (MWA) in order to accelerate reactions.



Scheme 1. Chiral auxiliary-mediated Pd-H reduction of imines **2** assisted by microwave irradiation.

Imines **2a**–**k** (Table 2) were obtained in yields around 75% from the corresponding acids (**3a**–**k**) and tryptamine by coupling with EDC/HOBt in CH_2Cl_2 at room temperature, which afforded the corresponding amides **5**. The amides **5a**–**k** were subjected to Bischler–Napieralsky cyclization affording imines **2a**–**k**.[2b,3–5] Having prepared imines **2** (Scheme 2), the next stage was set to introduce the asymmetry through the chiral auxiliaries and Pd-H reduction of the preformed *N*-acyliminium ions. It is well known that the Noyori asymmetric hydrogen-transfer reaction of imines.[6] Noyori and co-workers have shown that *p*-cymene–Ru(II) complexes of certain chiral 1,2-diamines are highly effective as catalysts for the asymmetric reduction of imines. This method uses a $HCO_2H–Et_3N$ azeotropic mixture as the hydrogen source and provides a convenient, general route to natural and unnatural β-carboline alkaloids. However, few alternatives are found for asymmetric β-carboline constructions based on imine systems.[2]

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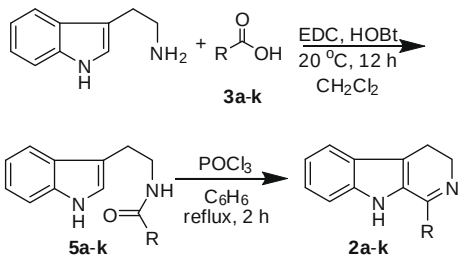
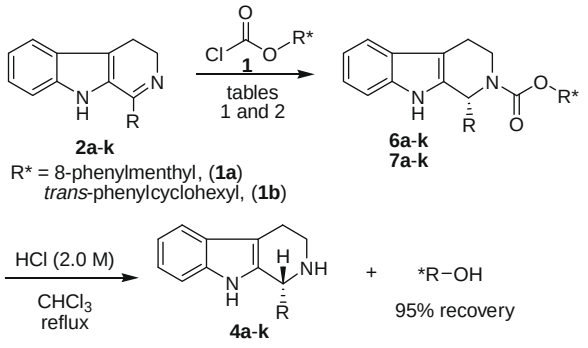


Scheme 2.

We first investigated the scope of reduction of imine **2a** mediated by chiral auxiliaries in an one-pot manner. The tested chiral auxiliaries were chloroformates of 8-phenylmenthyl (**1a**), and *trans*-phenylcyclohexanyl (**1b**), as depicted in Scheme 3. In situ formation of the corresponding *N*-acyliminium ions **8a** and **8b** from chloroformates of chiral auxiliary **1a**,**b,** and imine **2a**, followed by reduction afforded **6a** (R^* = 8-phenylmenthyl) and **7a** (R^* = *trans*-phenylcyclohexyl) in moderate to good yields (Table 1). Pd-H reductions of **8a** and **8b** were carried out using $PdCl_2/Et_3SiH$ protocol[7] at −78 °C, and compounds **6a** and **7a** were obtained in 87% and 75% yield, respectively (Table 1, entries 1 and 2). The diastereomeric ratio obtained employing palladium protocol were 6:1 for **6a** (Table 1, entry 1) and 4:1 for **7a** (Table 1, entry 2).

$NaCNBH_3$ was also employed as reducing agent in CH_2Cl_2/THF (2:1)[1g] as a solvent at −78 °C. Using $NaCNBH_3$, **6a** was obtained in 88% yield and 66% dr (5:1 *R*/*S*, entry 3), and **7a** in 73% yield and 50% dr (3:1 *R*/*S*, entry 4), respectively. $NaBH_4$ was also tested



Scheme 3.

Table 1
Reduction of imine **2a** to **6a**/**7a** by using chloroformates of 8-phenylmenthyl (**1a**) and *trans*-phenylcyclohexyl (**1b**) as chiral auxiliaries, and three different reducing agents

Entry	Chiral auxiliaries	Reducing agent[c] (condition)	Yield[a] (%)	Product dr[b]
1	**1a**	$PdCl_2/Et_3SiH$ (A)	87	**6a** 6:1 (*R*,*S*)
2	**1b**	$PdCl_2/Et_3SiH$ (A)	75	**7a** 4:1 (*R*,*S*)
3	**1a**	$NaCNBH_3$ (B)	88	**6a** 5:1 (*R*,*S*)
4	**1b**	$NaCNBH_3$ (B)	73	**7a** 3:1 (*R*,*S*)
5	**1a**	$NaBH_4$ (C)	90	**6a** 3:1 (*R*,*S*)
6	**1b**	$NaBH_4$ (C)	80	**7a** 2:1 (*R*,*S*)

[a] Isolated yields.
[b] Diastereomeric ratio (dr) calculated based on HPLC analysis of product **6a**.
[c] **A**: Chiral auxiliary, CH_2Cl_2, rt, 30 min, then $PdCl_2/Et_3SiH$, Et_3N, −78 °C, 1 h; **B**: chiral auxiliary, CH_2Cl_2, rt, 30 min, then $NaCNBH_3$/THF:CH_2Cl_2 (1:2), −78 °C, 1 h; **C**: chiral auxiliary, CH_2Cl_2, rt, 30 min, $NaBH_4$/THF:CH_2Cl_2 (1:2), 0 °C to rt, 1 h.

affording **6a** in 90% yield and 50% dr (entry 5), and **7a** in 80% yield, and 33% dr (entry 6), when CH_2Cl_2/THF (2:1) was used as solvent at 0 °C to 25 °C. The absolute configuration of the major compounds was determined to be (*R*) after removal of the chiral auxiliaries using $CHCl_3$/HCl (2.0 M) and reflux, which gave (+)-**4a** in yields around 90–95%. The enantiomeric excesses of major enantiomer (*R*)-(+)-**4a** obtained from **6a** and **7a** were >99% ee, as determined by HPLC analysis using a ChiralPack OD column, and it is in accordance with pure (*R*)-(+)-**4a** data.[3]

Table 1 shows that these one-pot reduction reactions to proceed efficiently by using CH_2Cl_2/THF (2:1) as solvent, when borohydrides are employed. The yields increased when the reaction was performed using $NaBH_4$ at ambient temperature, but with lower % dr. Chiral auxiliaries were recovered in 95% yield with no decrease of its optical rotations. Selectivity and the chiral auxiliary-mediated reduction of **2** was rationalized by the transition state depicted in Figure 1, which is in accordance with the reduction of the *N*-acyliminium ion **8** through its *Si*-face when **2** is used. The same model depicted in Figure 1 can be applied using **1b** as chiral auxiliary.

Next, we set out to employ MWA in the asymmetric reduction of **8**.[8] Microwave-assisted (MWA) conditions have been applied in a variety of synthetic transformations for time as well as energy-saving aspects.[9] In some cases, microwave-assisted irradiation is more selective in comparison to thermal reactions by favoring faster reactions and preventing decomposition of reactants and products.[10] Despite its increasing importance and recent usage, there are few reports on the application of MWA for the asymmetric reduction of imine groups.[11] Therefore, the aim of increasing the yields along with shortening of the reaction times, we decided to explore the MWA irradiation process as the heating source for the conversion of imines into respective chiral carbamates **6a**–**k** employing **1a** as chiral auxiliary. The same reaction condition as depicted in Table 1 (entry 1) was carried out under MWA irradiation in a sealed vessel. Reaction times were reduced to nine minutes for imines **6a**–**k**, the yields ranged from 65–90% and were compared to the thermal conditions, as shown in Table 2. Further, it was also observed that when applying the described protocol, the temperatures of the reaction mixture inside the reaction vessel reached values of 60 °C (9 min) for MWA irradiation reductions applying a potency of 90 W. Although these temperatures were higher than those used in the thermal conditions, times were shorter preventing in this way degradation of reactants and products, and favouring the enhancement of yields. The selectivities observed using MWA reductions were compared to thermal ones, and in some cases presented slight increase in the dr (Table 2, entries 2, 4, and 8).

The absolute configurations of **6a**–**k** were determined to be (*R*) after chiral auxiliary removal using HCl/$CHCl_3$ (2 M) that gave **4a**–**k** in 89–95% yields.[12] As mentioned above, the ee% for all amines **4** was >99% ee as determined by HPLC using a ChiralPack OD column, and it is in accordance with (*R*)-**4**.

In conclusion, a mild and efficient MWA methodology employing $PdCl_2/Et_3SiH$ for the preparation of β-carboline amines through

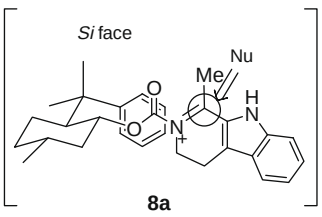
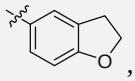


Figure 1. Proposed facial discrimination in the addition of Pd-H to the *N*-acyliminium ion derived from **2a** and **1a**.

Table 2
Microwave-assisted irradiation (90 W) and thermal reduction of imine **2** to **6** by using chloroformates of 8-phenylmenthyl (**1a**) as chiral auxiliary and $PdCl_2/Et_3SiH$ as reducing agent in CH_2Cl_2

Entry	Imine X (R)	MWA reaction		Thermal reaction	
		Time (°C)	**6**, dr[a] (yield %)[b]	Time (°C)	**6**, dr[a] (yield %)[b]
1	Me, **2a**	9 min (60 °C)	**6a**, 5:1 (90%)	0.5 (−78 °C)	**6a**, 6:1 (87%)
2	Et, **2b**	9 min (60 °C)	**6b**, 7:1 (85%)	1 (−78 °C)	**6b**, 6:1 (87%)
3	*iso*-Pr, **2c**	9 min (60 °C)	**6c**, 9:1 (82%)	3 (−78 °C)	**6c**, 12:1 (88%)[1c]
4	1-Pentenyl, **2d**	9 min (60 °C)	**6d**, 11:1 (78%)	3 h (−78 °C)	**6d**, 10:1 (85%)
5	Ph, **2e**	9 min (60 °C)	**6e**, 1:1 (65%)	1 h (−78 °C)	**6e**, 1.5:1 (85%)
6	Bn, **2f**	9 min (60 °C)	**6f**, 4:1 (75%)	1 h (−78 °C)	**6f**, 3.5:1 (90%)
7	$(CH_2)_2CO_2Me$, **2g**	9 min (60 °C)	**6g**, 5:1 (77%)	2 h (−78 °C)	**6g**, 5:1 (91%)
8	$(CH_2)_3CO_2Me$, **2h**	9 min (60 °C)	**6h**, 5.5:1 (80%)	2 h (−78 °C)	**6h**, 5:1 (89%)
9	$(CH_2)_7CH{=}CH(CH_2)_7Me$, (*Z*)-**2i**	9 min (60 °C)	**6i**, 7:1 (89%)	2 h (−78 °C)	**6i**, 8:1 (70%)
10	$(CH_2)_7(CH{=}CHCH_2)_4(CH_2)_3Me$, (*Z*,*Z*)-**2j**	9 min (60 °C)	**6j**, 9:1 (88%)	2 h (−78 °C)	**6j**, 10:1 (75%)
11	 , **2k**	9 min (60 °C)	**6k**, 12:1 (88%)	1 h (−78 °C)	**6k**, 13:1 (85%)[2b]

[a] Diastereomeric ratio (dr) calculated based on HPLC of product **6a**–**k**.
[b] Isolated yields.

chiral auxiliary induction has been developed. The $PdCl_2/Et_3SiH$ protocol is easy to manage, is inexpensive, safe to handle, stable, and is not pyrophoric, and no inert atmosphere is required. Interestingly, the MWA irradiation reactions presented similar yields with very short reaction times in contrast to the conventional thermal reactions. The reaction conditions are particularly attractive and are an example of a green chemistry approach due to performing reactions in a very short time period by MWA thereby reducing energy consumption, time savings, and increasing efficiency. If one compares the energy efficiency of conventional synthesis (heating/cooling by conduction and convection currents), and microwave-assisted reactions, it can be noted that for most chemical transformations a significant energy-saving (up to 80-fold) can be expected using microwaves as an energy source on a laboratory scale.[13]

Acknowledgments

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12. The NMR spectroscopic data for all compounds are in accordance with previously described for **4a**–**k**. Optical rotations obtained for majoritary *R* compounds are as follows: *Compound* **4a**: $[\alpha]_D$ +51 (*c* 1.0, MeOH). *Compound* **4b**: $[\alpha]_D$ +62.0 (*c* 1.0, MeOH). *Compound* **4c**: $[\alpha]_D$ +66 (*c* 1.0, MeOH). *Compound* **4d** was not previously described: $[\alpha]_D$ −25.0 (*c* 1.0, $CHCl_3$). FT-IR (KBr film) cm^{-1}: 3409, 3218, 3062, 2929, 2844, 2744, 1641, 1562, 1452, 1343, 1317, 1288, 1155, 1108, 1002, 909, 744. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.70 (3H, m), 1.84–1.91 (1H, m), 2.09–2.19 (2H, m), 2.68–2.80 (1H, m), 2.75 (1H, dq, *J* 8.0, 1.9), 3.03 (1H, ddd, *J* 15.5, 8.0, 5.5), 3.34 (1H, dt, *J* 14.5, 4.5), 4.07 (1H, br s), 4.98 (1H, br d, *J* 10.2), 5.03 (1H, dd, *J* 17.1, 1.6), 5.80 (1H, ddt, *J* 17.1, 10.2, 6.7), 7.09 (1H, dt, *J* 7.6, 0.7), 7.14 (1H, dt, *J* 7.6, 0.7), 7.30 (1H, d, *J* 7.8), 7.47 (1H, d, *J* 7.8), 7.84 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 25.0, 33.7, 34.3, 42.5, 52.5, 109.0, 110.7, 115.0, 118.0, 119.3, 121.5, 127.5, 135.6, 136.1, 138.3. HRMS, ESI(+)-MS: *m*/*z* calcd for $[C_{16}H_{20}N_2+H]^+$: 241.1705, found: 241.1701. *Compound* **4e**: $[\alpha]_D$ −4.0 (*c* 1.0, $CHCl_3$). *Compound* **4f**: $[\alpha]_D$ −55.0 (*c* 1.0, MeOH). *Compound* **4g** (tetracyclic lactam obtained after chiral auxiliary removal):[3] $[\alpha]_D$ +240.5 (*c* 1.0, $CHCl_3$). *Compound* **4h** (tetracyclic lactam obtained after chiral auxiliary removal):[3] $[\alpha]_D$ +260.5 (*c* 1.0, $CHCl_3$). *Compound* **4i** was not previously described: $[\alpha]_D$ +20.0 (*c* 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* 7.0 Hz), 1.20–1.41 (20H, m), 1.41–1.58 (2H, m), 1.64–1.76 (1H, m), 1.81–1.92 (1H, m), 1.93–2.02 (5H, m), 2.72–2.78 (2H, m), 3.02–3.07 (1H, m), 3.33–3.37 (1H, m), 4.05–4.09 (1H, m), 5.29–5.40 (2H, m), 7.09–7.15 (2H, m), 7.31 (1H, d, *J* 8.0 Hz), 7.49 (1H, d, *J* 8.0 Hz), 7.92 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.3, 22.6, 25.8, 27.2, 27.25, 29.2, 29.3, 29.4, 29.5, 29.55, 29.7, 29.8, 29.85, 32.0, 34.9, 42.3, 52.8, 108.7, 110.8, 118.0, 119.4, 121.6, 127.3, 129.7, 130.0, 135.6, 135.70. HRMS, ESI(+)-MS: *m*/*z* calcd for $[C_{28}H_{44}N_2+H]^+$: 409.3583, found: 409.3578. *Compound* **4j** was not previously described: $[\alpha]_D$ +12.0 (*c* 1.0, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* 7.0 Hz), 1.26–1.35 (6H, m), 1.52–1.66 (2H, m), 1.71–1.79 (1H, m), 1.86–1.94 (1H, m), 2.03–2.16 (5H, m), 2.75–2.88 (8H, m), 3.05–3.12 (1H, m), 3.34–3.39 (1H, m), 4.18 (1H, br s), 5.31–5.39 (8H, m), 7.07–7.14 (2H, m), 7.31 (1H, d, *J* 8.0 Hz), 7.47 (1H, d, *J* 8.0 Hz), 7.48 (1H, d, *J* 8.0 Hz), 7.93 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 21.8, 22.7, 25.6, 25.7, 25.75, 25.76, 27.1, 27.2, 29.5, 31.5, 34.0, 42.1, 52.6, 108.5, 110.8, 118.1, 119.7, 121.7, 127.3, 127.5, 127.9, 128.1, 128.3, 128.6, 128.7, 129.4, 130.6, 135.7, 136.0. HRMS, ESI(+)-MS: *m*/*z* calcd for $[C_{30}H_{42}N_2+H]^+$: 431.3426, found: 431.3430. *Compound* **4k**: $[\alpha]_D$ +23.0 (*c* 1.0, MeOH).
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