Synthetic Methods

DOI: 10.1002/ange.200501745

Enantioselective α-Arylation of Cyclohexanones with Diaryl Iodonium Salts: Application to the Synthesis of (−)-Epibatidine**

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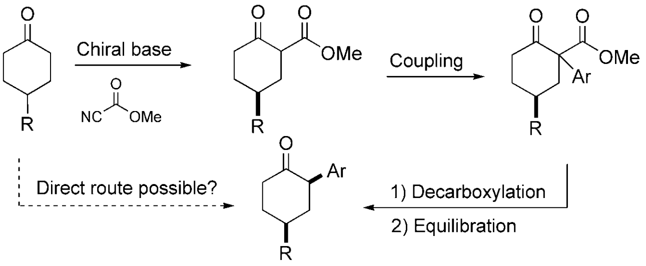
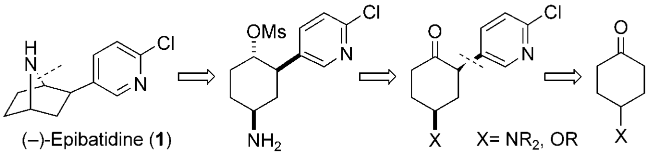
The enantioselective introduction of electrophiles α to carbonyl groups is a central topic in asymmetric synthesis. Although asymmetric α-alkylations have been well developed, high enantioselectivity in α-arylation of ketones has only been achieved in a very limited number of cases. These involve arylation of trisubstituted enolates using binap–Pd complexes which gives non-epimerizable, tetrasubstituted ketones.[1,2] However, this strategy cannot be used in the desymmetrization/arylation of cyclic ketones, since even if the enolate was generated enantioselectively, the ketone product would racemize the starting enolate (through proton transfer) at the high temperatures required for arylation.

An alternative strategy involves α-arylation of β-ketoesters with aryl lead reagents (Scheme 1).[3] This strategy can be rendered asymmetric through 1) desymmetrization/β-ketoester formation,[4] 2) arylation,[3] and 3) decarboxylation and subsequent equilibration.



Scheme 1. Possible asymmetric routes toward 2-aryl cyclohexanones.

However, a direct asymmetric arylation of cyclohexanones would clearly be superior. If this could be achieved, we envisaged that this strategy could be applied to a short asymmetric synthesis of the alkaloid (−)-epibatidine (**1**) (Scheme 2). Herein, we describe our success in achieving these goals.

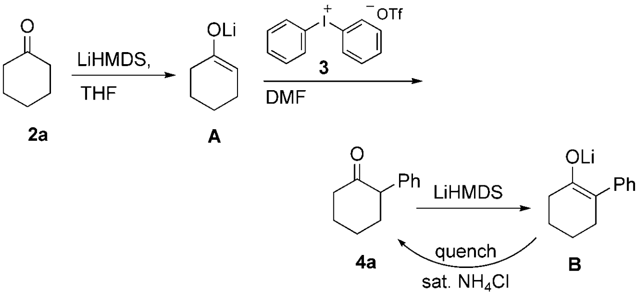


(−)-Epibatidine (**1**)

Scheme 2. Retrosynthesis of (−)-epibatidine.

As possible electrophilic sources of aryl reagents, we considered diaryl iodonium(III) salts since scattered reports existed of couplings with silyl enol ethers,[5] ketones,[6] and malonates,[7] albeit with varying yields. The scope and limitations of these couplings had not been investigated, and no successful asymmetric reactions have been reported.[8] Indeed, the dearth of examples of enolate arylations with diaryl iodonium(III) salts encouraged us to explore this area further.

The coupling conditions were optimized with cyclohexanone (**2a**) and the commercially available diphenyl iodonium salt **3** (Scheme 3).[9] Under optimized conditions arylation of cyclohexanone (**2a**) gave **4a** in 83% yield (entry 1, Table 1). It should be noted that 2 equivalents of base are required; the second equivalent is used to deprotonate the product ketone.[10] Despite the fact that part way through the reaction enolates **A** and **B** are both present, no bis-arylated product was observed under our optimized conditions (Scheme 3).[11]



2a **A** **3** **4a** **B**

Scheme 3. α-Arylation of cyclohexanone (**2a**); HDMS = hexamethyldisilazide.

When applied to 4-substituted cyclohexanones **2b–d**, the coupling reaction afforded 2,4-disubstituted products **4b–d** in high yields and with high diastereoselectivities (Table 1).[12] As expected, arylation of *tert*-butyl ketone **2b** resulted in **4b** with high *cis* selectivity (entry 2), whilst ketone **2c** yielded a 5:1 *cis*/*trans* mixture (entry 3). In contrast, reaction of the 4-silyloxy ketone **2d** led to **4d** with high *trans* selectivity, the 4-OTBDMS occupying the axial position (entry 4). It has been suggested that an attractive electrostatic interaction and/or an n,π* orbital overlap between the silyloxy group and the carbonyl carbon favors the axial orientation of 4-alkoxy substituents and so the *trans* isomer is likely to be the

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[**] We thank Merck and the Swedish Research Council for financial support.

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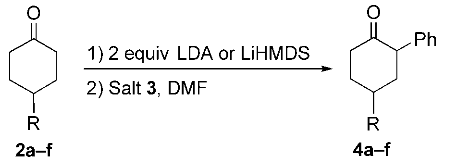
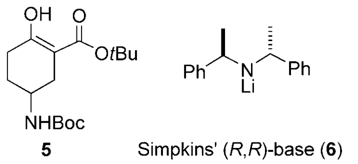
Table 1: Couplings of ketones **2** and diphenyl iodonium salt **3**.[a]



Entry	Ketone (R)	Base	Yield of **4** [%][b]	*cis/trans*
1	**2a** (H)	LHMDS	83	–
2	**2b** (*t*Bu)	LDA	69	>20:1
3	**2c** (Ph)	LDA	76	5:1
4	**2d** (OTBDMS)	LDA	70	1:15
5	**2e** (NBoc$_2$)	LHMDS	18[c]	>20:1
6	**2f** (NHBoc)	LDA	31[d]	10:1

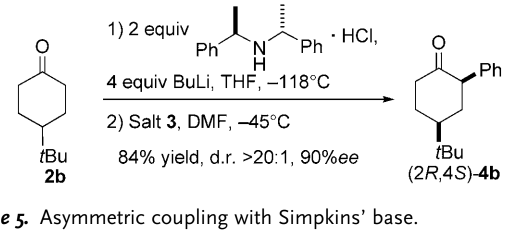
[a] Conditions: The ketone was treated with LHMDS or LDA at −78 °C in THF. Salt **3** was added in DMF and the reaction was stirred at −45 °C for 4–5 h. LDA = lithium diisopropylamide, TBDMS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl. [b] Yields of isolated products. [c] The major product was Boc-transfer product **5**, see text. [d] 2,2-Diphenyl-4-NHBoc ketone (38 %) and **2f** (30 %) were also isolated.

thermodynamically more stable product.[13,14] Application of this methodology to 4-aminoketone **2e**[15] was complicated by an unexpected intramolecular Boc-transfer reaction, yielding enol ester **5** as the major product (37 %) (entry 5 and Scheme 4).[16] The Boc-transfer could be avoided by employing ketone **2f**, but the yield of **4f** was moderate due to competitive deprotonation of the carbamate nitrogen.[17] This entry shows that enolate **B** (Scheme 3) can indeed react to give disubstituted product when enolate **A** is absent, as the major product in this case was the corresponding diphenyl compound (38 %).



Scheme 4. Boc-transfer product **5** and chiral base **6** used in asymmetric reactions.

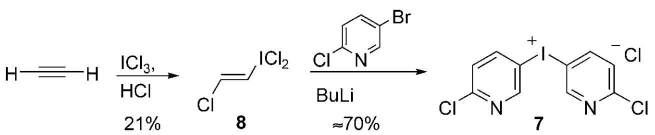
Employing Simpkins' (*R*,*R*)-base (**6**; Scheme 4) instead of LDA or LHMDS, we found that *tert*-butylcyclohexanone (**2b**) gave the arylated product (2*R*,4*S*)-**4b** in 84 % yield and 90 % enantiomeric excess (Scheme 5).[18] The enantioselectivity was in the range typical for this class of desymmetrization,[19,20] which clearly indicates that proton transfer between the product and the starting enolate was not occurring. Had this occurred, lower enantioselectivity would have been expected because the second equivalent of base would have deprotonated the ketone at −45 °C instead of −118 °C. Evidently, the second equivalent of base acted to directly deprotonate the arylated ketone.



Scheme 5. Asymmetric coupling with Simpkins' base.

Having established the asymmetric methodology for the α-arylation of cyclic ketones, we sought to apply it to a short enantioselective synthesis of epibatidine (**1**; Scheme 2). This alkaloid, which was isolated from the Ecuadorian poison frog *Epipedobates tricolor* in 1993, is 400 times more potent than morphine as an analgesic, and is also an extremely potent agonist of the nicotinic acetylcholine receptor.[21] Numerous syntheses of epibatidine have since been published, most of which are racemic.[22] One commonly employed strategy to introduce the pyridyl group involves an organometallic coupling with a 2-halosustituted cyclohexanone,[23,24] a reaction that cannot be rendered asymmetric (since the starting material is already chiral). As depicted in our retrosynthesis (Scheme 2), the direct coupling of a 4-substituted cyclohexanone with a pyridyl iodonium salt not only shortens the synthetic pathway but also renders the synthesis asymmetric.

Our strategy required a pyridyl iodonium salt that had not been previously prepared. After some experimentation, pyridyl salt **7** was synthesized in good yield from compound **8** and commercially available 2-chloro-5-bromopyridine (Scheme 6).[25]

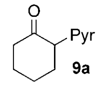
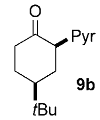
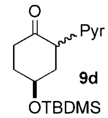
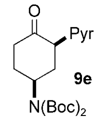


Scheme 6. Synthesis of pyridyl iodonium salt **7**.

Various cyclohexanones were treated with chiral base **6** and coupled with salt **7**, leading to the corresponding arylated ketones with high enantioselectivities and moderate to good yields (Table 2).[22,26] The pyridyl group on the iodonium salt had a negative impact on the yield of the coupling of ketones **2a** and **2b**. Whilst the diphenyl iodonium salt **3** gave **4a** in 83 % yield, the pyridyl iodonium salt **7** only gave a 51 % yield of coupling product **9a** (entry 1, Tables 1 and 2 respectively). Fortunately ketones **2d** and **2e**, both possible precursors to epibatidine, proved to be better substrates in the coupling reaction with the pyridyl iodonium salt **7**. Ketone **2d** has been previously employed in asymmetric desymmetrization reactions.[19,27] When this substrate was treated with base **6** and coupled with iodonium salt **7**, 2-pyridyl ketones **9d** were obtained in good yield and high enantioselectivity (entry 3). Interestingly, whilst the 2-phenyl ketone **4d** was formed with high *trans* diastereoselectivity (Table 1, entry 4), the 2-pyridyl ketone **9d** was produced with modest *cis* selectivity.[28]

Although asymmetric desymmetrization of ketone **2e** had not been previously reported, we expected that the steric bulk provided by the N(Boc)$_2$ moiety would lock the conformation of the cyclohexanone ring and thus lead to good asymmetric induction. Indeed, enantioselective deprotonation with base **6** and subsequent coupling afforded pyridyl ketone **9e** in 41 %

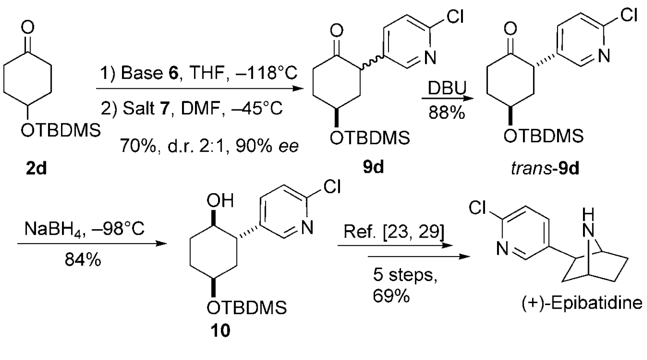
Table 2: Asymmetric couplings with pyridyl iodonium salt **7**.[a]

Entry	Ketone	Product[b]	Yield [%][c]	*ee* [%]
1	**2a**	 **9a**	51	–
2	**2b**	 **9b**	51	90
3	**2d**	 **9d**	70[d]	90
4	**2e**	 **9e**	41[e]	86 (94)[f]

[a] Conditions: The ketone was treated with base **6** at −118 °C in THF (entry 1: LHMDS at −78 °C). A solution of salt **7** in DMF was added and the reaction was stirred at −45 °C for 4 h. [b] Pyr = 5-(2-chloropyridyl). [c] Yields of isolated products. [d] *cis/trans* 2:1, 13% recovered **2d**. [e] Compound **5** isolated in 14% yield. [f] After recrystallization.

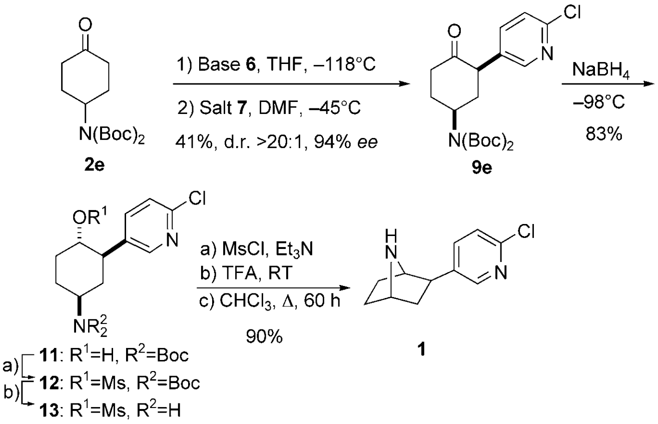
yield and 86% *ee* with complete *cis* selectivity (entry 4). Furthermore, a single recrystallization enhanced the enantiomeric excess of **9e** to 94%. This result indicates that salt **7** is more reactive than the diphenyl salt **3**, as much less of the Boc-transfer product was observed in this reaction.

Having established the asymmetric α-arylation reaction we proceeded to complete the synthesis of epibatidine with ketones **2d** and **2e**. Commercially available ketone **2d** was employed in a formal synthesis of (+)-epibatidine (Scheme 7). As discussed above, the asymmetric iodonium coupling afforded 2-pyridyl ketone **9d** as a kinetically formed 2:1 *cis/trans* mixture, which was equilibrated with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to afford a separable 1:4 mixture with *trans*-**9d** as the major diastereomer. Ketone *trans*-**9d** was subsequently reduced with sodium borohydride to give the corresponding equatorial alcohol **10** in 84% isolated yield (d.r. 10:1 in crude). Alcohol **10** has previously been transformed into epibatidine in a further five steps,[23,29] thus providing a short and high-yielding formal synthesis of (+)-epibatidine. The optical rotation of **10** revealed that although the 4-OTBDMS group in **2d** prefers the axial conformation, it must be the *equatorial* conformation that becomes deprotonated by the chiral base.[30]



Scheme 7. Formal synthesis of (+)-epibatidine.

Alternatively, transformation of ketone **2e** to naturally occurring (−)-epibatidine could be performed in five straightforward steps (Scheme 8). 2-Pyridyl ketone **9e** was formed with high enantiomeric excess, as discussed above, and reduced to alcohol **11** using sodium borohydride at low temperature with high diastereoselectivity (d.r. 7:1 in crude). Compound **11** was converted into (−)-epibatidine ($[\alpha]_D^{20} = -6.2$ ($c = 0.21$, CH_2Cl_2); literature value:[22b] $[\alpha]_D^{25} = -6.7$ ($c = 0.21$, CH_2Cl_2)) by sequential mesylation, deprotection and ring-closure in 90% yield over the three steps.[31] The total synthesis was thus accomplished in six steps and 31% overall yield from commercially available **2f** with essentially complete control of diastereoselectivity, thus providing the shortest and most efficient asymmetric route to this important compound to date.[32]



Scheme 8. Synthesis of (−)-epibatidine. Ms = methanesulfonyl, TFA = trifluoroacetic acid.

In summary, a direct asymmetric α-arylation of cyclohexanones has been developed. The method employs Simpkins' base to desymmetrize 4-substituted cyclohexanones by asymmetric enolization followed by coupling with diaryl iodonium salts, leading to 2-aryl ketones in moderate to good yields and high enantioselectivities. The method expands the scope of the desymmetrization strategy pioneered by Simpkins and Koga, and highlights the utility of iodonium salts for aryl transfer reactions in synthesis. This approach has been applied in a short and efficient total synthesis of (−)-epibatidine and a formal synthesis of (+)-epibatidine.

Received: May 20, 2005

Keywords: cyclohexanone · desymmetrization · enolates · epibatidine · iodonium salts

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[8] One report of a coupling between a chiral diaryl iodonium salt and cyclic β-keto esters bearing chiral auxiliaries resulted in modest *ee*'s, see M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233.

[9] The iodide salt was also tested and gave similar yields to the triflate salt.

[10] Both LiHMDS and LDA could be successfully employed, LiHMDS gave generally slightly higher yields.

[11] Significant double arylation was obtained at low temperature (up to 31 %) but above −45 °C only monoarylation was observed.

[12] The diastereoselectivity of the initial coupling is irrevelant, as the product is immediately deprotonated by the second equivalent of base, see Scheme 3. The diastereoselectivity is determined during the protonation (in the quench) under kinetic conditions.

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[14] In the parent ketone, the C4 proton appears as a triplet of triplets in the ^{1}H NMR spectrum, $J = 5.2$ and 4.7 Hz, indicative of a predominant axial conformation of the silyloxy substituent.

[15] **2e** was obtained from commercially available NHBoc ketone **2f** by Boc-protection in quantative yield, see the Supporting information.

[16] When **2e** was treated with LDA without addition of iodonium salt, compound **5** was isolated in 75 % yield. The intramolecular nature of the reaction was proved by a cross-over experiment with cyclohexanone. Only **5** and cyclohexanone were isolated; *tert*-butyl 2-oxocyclohexanecarboxylate was not observed.

[17] Ketone **2f** could be recovered in 30 %. Use of 3 equiv base did not increase the yield of **4f**, instead more byproducts were formed.

[18] The enantiomeric excess was measured by chiral HPLC, see Supporting information. Absolute configurations were assigned by analogy with previous desymmetrizations of cyclohexanones with Simpkins' base.

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[25] A modified procedure was developed from a) P. J. Stang, B. Olenyuk, K. Chen, *Synthesis* **1995**, 937; b) F. M. Beringer, R. A. Nathan, *J. Org. Chem.* **1969**, *34*, 685, see Supporting information. An unsymmetrical pyridyl-phenyl iodonium salt was also prepared, but this gave consistently lower yields in the couplings due to moderate selectivity of pyridyl-group transfer compared to phenyl transfer.

[26] The 2-chloro-5-iodopyridine formed from **7** can be recovered and used in the synthesis of **7**.

[27] M. Majewski, N. M. Irvine, J. MacKinnon, *Tetrahedron: Asymmetry* **1995**, *6*, 1837.

[28] The moderate diastereoselectivity could be explained by a diminished preference for the axial position in the enolate intermediate **A** (Scheme 1), which is quenched to give the product mixture.

[29] a) E. Albertini, A. Barco, S. Benetti, C. De Risi, P. Pollini, R. Romagnoli, V. Zanirato, *Tetrahedron Lett.* **1994**, *35*, 9297; b) A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Eur. J. Org. Chem.* **2001**, 975.

[30] Analytical data were in agreement with literature. Optical rotation differed in magnitude with the literature but had the same sign. Value observed by us: $[\alpha]_D = -7.2$ ($c = 0.32$, CH_2Cl_2); literature value:[23] $[\alpha]_D = -10.6$ ($c = 0.32$, CH_2Cl_2).

[31] The conversion of alcohol **11** to epibatidine follows the sequence described for the corresponding NHBoc compound.[24] Analytical data of **1** (see Supporting information) were in agreement with those reported in ref. [22].

[32] Compare ref. [22]; a) 9 steps, 21 % yield; b) 13 steps, 13 % yield; d) 10 steps, 5.9 % yield.