Highly enantioselective Mannich reaction of aldehydes with cyclic N-acyliminium ions by synergistic catalysis

Francesco Berti,[a] Federico Malossi,[a] Fabio Marchetti,[b] and Mauro Pineschi*[a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Matched combinations of Brønsted or Lewis acids with suitable pro-electrophiles and secondary amine organocatalysts enable novel enantioselective syntheses of carbamoyl dihydroquinoline and tetrahydropyridine derivatives with concomitant formation of two stereocenters. A short formal asymmetric synthesis of (2*R*, 2'*R*)-*threo*-methylphenidate (Ritalin) is also described.

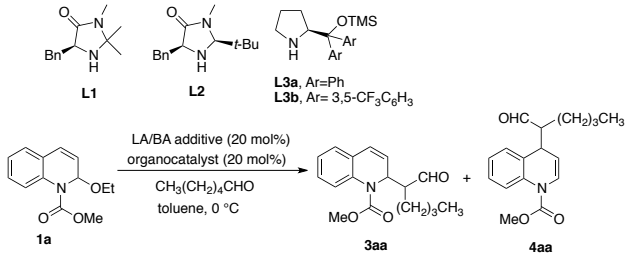
Organocatalytic enantioselective Mannich reactions using highly reactive N-acyliminium ions has been exploited using various aromatic and heteroaromatic C-nucleophiles mainly using chiral Brønsted acid catalysts.[1] On the other hand, the use of a chiral enamine in combination with N-acyliminium ions is usually problematic in view of the high reactivity of these unstable intermediates and the possible deactivation of the chiral amine-based organic catalysts by acylation. Notwithstanding solutions to this problem were recently reported for isoquinolines,[2] the direct functionalization of N-acyliminium ions derived from dihydroquinolines and tetrahydropyridines with aldehydes has remained elusive. In particular, functionalized piperidines are very popular compounds widespread in a number of biologically active molecules.[3] In principle, the intermolecular enantioselective addition of carbon nucleophiles to pyridinium ions represents a direct entry to these scaffolds which has been achieved so far with the aid of transition metal catalysts.[4,5] In fact, the organocatalyzed addition of carbonyl compounds to six-membered cyclic imine/iminium ion intermediates is a notoriously challenging process with many limitations, such as very long reaction times and difficult accessibility and stability of the cyclic imine.[6] To the best of our knowledge, no example of catalytic asymmetric alkylation of non-aromatic six-membered N-acyliminium ion with aldehydes has been reported to date. We envisioned that a one-pot enamine /cylic acyliminium intermediate formation without a concomitant acylation of the secondary amine catalyst might be feasible by means of synergistic Brønsted acid (BA) or Lewis acid (LA) catalysts starting from suitable stabilized non-electrophilic precursors.[7] We herein report a simple α-alkylation of aldehydes by the *in situ* generation of reactive cyclic N-acyliminium electrophiles starting from stable and easily available compounds to give 1,2-dihydroquinolines and 1,2,5,6-tetrahydropyridines containing two stereogenic centers in enantioenriched manner.

In continuation of our interest in Mannich-type reactions using (hetero)cyclic iminium ions,[8] at the outset of this research we envisioned the possibility to use 2-ethoxy-1-methoxycarbonyl-1,2-dihydroquinoline **1a** as pro-electrophile in combination with LA/BA, hexanal and organocatalysts reported in Table 1. Differently from related isoquinoline N,O-acetal,[2b,c] control experiments carried out without the use of LA/BA additives did not afford alkylation products **3aa** and **4aa**. Unreacted starting N,O-acetal **1a** and quinoline (**Q**) derived from its decomposition were recovered (Table 1, entries 1 and 2). On the other hand, MacMillan catalysts **L1** and **L2** proved to be capable of catalysing this reaction in few hours at 0 °C using different Lewis acids (entries 3-8). In particular, the reactions carried out in THF showed improved results with these imidazolidinone organocatalysts (entries 7 and 8). This result was rather surprising considering the known lower nucleophilicity of the enamine derived from these organocatalysts and the complete absence of reactivity observed in the reaction with isoquinoline derivatives.[2b,c] Hayashi-Jørgensen secondary amine catalysts **L3a,b** afforded the corresponding 1,2-adduct **3a**-*syn* with average higher diastereo- and enantioselectivities, albeit with longer reaction times (entries 9 and 10). After extensive examination, it was found that the use of *p*-toluensulfonic acid (TsOH) had a beneficial effect on stereoselectivities (entries 13 and 14). In particular, using this additive in combination with catalyst **L3b**, the formation of quinoline was dramatically reduced to indicate maximum efficiency of the aldehyde alkylation by synergistic catalysis (entry 14).[9] On the other hand, the use of other acid additives resulted in lower diastereo- and enantioselectivities (entries 15-17).

Table 1. Screening of reaction conditions.[a]

[a] *Dipartimento di Farmacia, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy.*
[b] *Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via G. Moruzzi 3, 56124, Pisa, Italy.*

Electronic Supplementary Information (ESI) available: Experimental procedure, expanded Tables, characterization data, ^{1}H, ^{13}C NMR spectra, and a CIF file of compound **5dc**-*syn*. See DOI: 10.1039/x0xx00000x



Entry	Cat	LA/BA	**3/4/Q**[b]	dr (*syn*/*anti*)[b]	ee (*syn*)[c]
1	**L1**	none	No reaction		-
2	**L3a**	none	No reaction		-
3[d]	**L1**	$In(OTf)_3$	69/11/20	61/39	68
4[d]	**L1**	$Yb(OTf)_3$	70/10/20	56/44	60
5	**L1**	$MgBr_2$	48/12/40	66/34	29
6	**L2**	$In(OTf)_3$	66/27/7	42/58	66
7[d,e]	**L2**	$In(OTf)_3$	79/15/6	51/49	94
8[d,e]	**L2**	$InBr_3$	83/13/7	58/42	74
9	**L3a**	$In(OTf)_3$	71/14/15	79/21	94
10	**L3b**	$In(OTf)_3$	80/5/15	74/26	92
11[e]	**L3a**	$In(OTf)_3$	57/6/37	60/40	58
12[f]	**L3a**	$In(OTf)_3$	65/13/22	74/26	92
13	**L3a**	TsOH	62/8/30	84/16	96
14	**L3b**	TsOH	90/7/3	82/18	96
15	**L3a**	$PhCO_2H$	72/9/19	86/14	65
16	**L3a**	TFA	41/5/54	70/30	92
17	**L3b**	TfOH	83/9/8	57/43	54

[a] All reactions were carried out at 0 °C using 0.15 mmol of **1a**, 20 mol% LA/BA, 20 mol% organocatalyst, hexanal (0.6 mmol), toluene (0.6 mL) at 0 °C for 18h, followed by aqueous workup, unless stated otherwise. **Q** = quinoline. [b] Regioselectivity and *syn/anti* ratio of the 1,2-adduct **3aa** determined by ^{1}H NMR of the crude mixture. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction time 3h. [e] Reaction carried out in THF. [f] Reaction carried out in CH_2Cl_2.

It should be noted that the alkylation reaction can be also carried out in CH_2Cl_2 with easily available preformed quinolinium ion **A** (*vide infra* Figure 2, X = OTf, PG = COOEt). In this case, the corresponding *syn/anti* adduct **3ba** was obtained with a low yield of 50% and with 63/47 d.r. (44% ee for *syn* and 54% ee for *anti*-adduct), in line with the result obtained using the corresponding N,O-acetal pro-electrophile **1a** and hexanal (Table 1, entry 17). In general, 1,2-adduct **3aa**-*syn* and **3aa**-*anti* proved to be stable but unseparable by chromatographic purification on silica gel.[10] The negative result of an epimerization test carried out by treating the mixtures of *syn/anti* diastereoisomers **3aa** with 20 mol% of **L3a** for 4 days at rt indicated that the reaction is under kinetic control.

The optimized reaction conditions were applied to a broader range of aldehydes and quinoline N,O-acetals and the results are summarized in Table 2. In most cases it was necessary to perform in situ reduction of *syn*/*anti* mixtures of aldehydes of type **3** to determine the enantiomeric enrichment by HPLC on chiral stationary phases. This reduction allowed in some cases a chromatographic purification of the corresponding *syn* and *anti* diastereoisomeric alcohols of type **5** (entries 2, 3,5,6 and 8). The optimized reaction conditions were particularly successful with phenyl acetaldehyde (entries 2, 6, 8 and 11) delivering the corresponding functionalized dihydroquinolines in short reaction times (1-3 h at 0 °C) with moderate to good yields and high ees. Also linear aliphatic aldehydes gave good results (entries 3, 4, 7, 9, 10 and 12-14), while the use of acetaldehyde afforded alkylated products with moderate yields and low ees (entries 1 and 5).[2b] Average longer reaction times but high enantioselectivities were obtained with 6-substituted quinolines with both electron-withdrawing and electron-donating substituents (entries 8-13). Interestingly, excellent enantiocontrol was observed with 4-methyl substituted quinoline **1h** (entry 14), whereas 4,7-dichloroquinoline derivative **1i** proved to be not effective (data not reported in Table 2).

The relative and absolute configuration of the newly created chiral centers were unequivocally determined by single crystal X-ray analysis of compound **5dc**-*syn* (Table 2, entry 7) (Figure 1).[11]

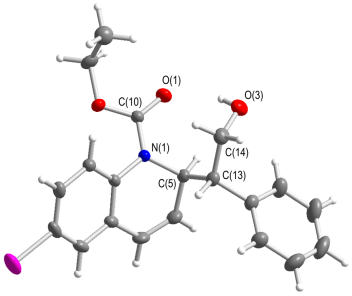


Figure 1. ORTEP diagram of compound **5dc**-*syn.* Ellipsoids are at 30% probability.

The synergistic catalysis hypothesized in this study requires a concomitant activation of the aldehyde and *pro-electrophile* **1** using two distinct and both necessary catalysts (*i.e* a secondary amine and a Lewis/Brønsted acid) to give the corresponding reactive species **B** and **A** (Figure 2). Control ^{1}H NMR experiments carrying out the reaction in toluene-d_8 with organocatalyst **L4b** and propanal showed that quinolinium ion **A** and prolinol ether enamine **B** cannot be detected.[12]

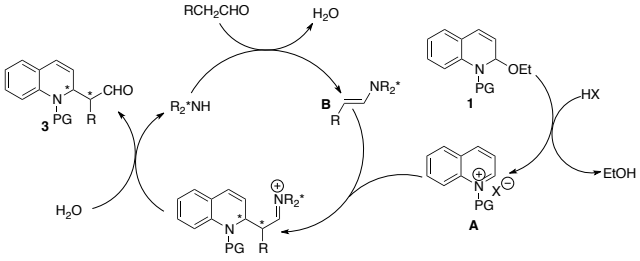


Figure 2. Plausible mechanism for the synergistic catalysis.

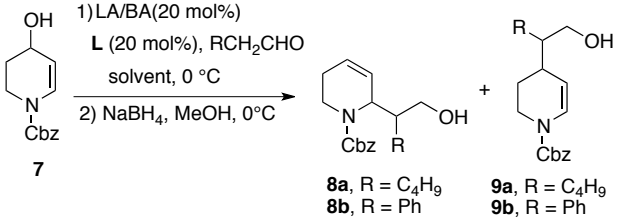
Table 2. Organocatalyzed alkylation of quinoline N,O-acetals **1a-f** using different aldehydes.[a]

N°	Y	PG	R	Product, Yield %[b]	Dr[c]	Ee[d] (*syn*)
1	H	CO_2Me	H	**5ab**, 75	Na	11
2	H	CO_2Me	Ph	**5ac**-*syn*, 58	77/23	96
3	H	CO_2Me	CH_3	**5ad**-*syn*, 81	83/17	98
4	H	CO_2Et	C_4H_9	**3ba**, 85[g]	78/22	83
5	H	Cbz	H	**5cb**-*syn*, 80	Na	25
6	H	Cbz	Ph	**5cc**-*syn*, 50	77/33	96
7[e]	H	Cbz	CH_3	**5cd**, 80[g]	80/20	62
8	6-Br	CO_2Et	Ph	**5dc**-*syn*, 36	73/27	98
9[f]	6-Br	CO_2Et	C_4H_9	**3da**, 80[g]	71/29	99
10	6-NO_2	CO_2Et	CH_3	**5ed**, 70[g]	65/35	91
11	6-NO_2	CO_2Et	Ph	**5ec**, 78[g]	70/30	97
12	6-OMe	CO_2Et	C_4H_9	**5fa**, 52[g]	65/35	90
13	6-Me	CO_2Et	C_4H_9	**3ga**, 87[g]	71/29	99
14	4-Me	CO_2Et	C_4H_9	**5ha**, 88[g]	63/37	99

[a] Unless stated otherwise all reactions were carried out at 0 °C for 1-5 h. [b] Isolated yield of indicated compound. [c] *Syn/anti* ratio determined by ^{1}H NMR of the crude mixture. [d] Ee of the *syn*-adduct after chromatographic purification on SiO_2 (see ESI for further details on this Table). [e] Reaction carried out for 18h at 0 °C. [f] Reaction carried out for 24h at rt. [g] Isolated yield of unseparable mixtures of *syn*/*anti* diastereoisomers.

The individuation of reaction condition for the enantioselective alkylation of six-membered non-aromatic N-acyliminium ions with aldehydes showed to be less straightforward. No aldehyde alkylation was observed using a variety of N-acyliminium precursors and reaction conditions both using LA or BA additives.[13] To our delight, after extensive examination, a solution was found by the use of vinylogous γ-hydroxy derivative **7** (Table 3). Differently from N-acyl quinolinium **1a**, pro-electrophilic substrate **7** showed to be unreactive with hexanal in combination with BA/LA and pyrrolidine type catalysts **L3a,b** (entries 1-4). On the other hand, imidazolidinone catalysts **L1** in combination with $In(OTf)_3$ in THF afforded the corresponding alkylated N-carbamoyl tetrahydropyridine **8a** (R = C_4H_9) with high enantioselectivity albeit with a low yields and diastereoselectivity (entry 5).

Table 3. Screening of reaction conditions.[a]

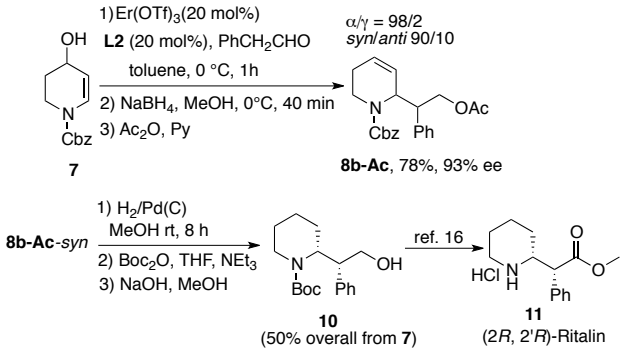


Entry	Cat	LA/BA	**8/9**[d]	Dr[e] *Syn/anti*	Y[f]	Ee[g] *Syn/anti*
1[b]	**L3a**	$In(OTf)_3$	nd	nd	<5	nd
2[b]	**L3b**	TsOH	nd	nd	<5	nd
3[b]	**L3a**	$In(OTf)_3$	nd	nd	<5	nd
4[b]	**L3b**	TsOH	nd	nd	<5	nd
5[b]	**L1**	$In(OTf)_3$	95/5	51/49	35	91/70
6[b]	**L2**	$In(OTf)_3$	95/5	55/45	40	82/40
7[c]	**L2**	$In(OTf)_3$	95/5	88/12	65	88/20
8[c]	**L2**	$MgBr_2$	nd	nd	<5	nd
9[c,h]	**L2**	$Yb(OTf)_3$	72/28	77/33	60	94/82
10[c]	**L2**	AgOTf	93/7	73/27	72	90/74
11[c]	**L2**	$Ce(OTf)_3$	96/6	80/20	50	84/60
12[c]	**L2**	$Er(OTf)_3$	98/2	90/10	78	93/70
13[c]	**L2**	$Eu(OTf)_3$	99/1	69/31	79	92/80
14[c]	**L2**	$InBr_3$	76/24	88/12	65	88/90

[a] Reactions were carried out at 0 °C using 0.15 mmol of **7**, 20 mol% LA/BA, 20 mol% organocatalyst, aldehyde (0.6 mmol), solvent (0.6 mL) at 0 °C, followed by aqueous workup. [b] Reactions carried out in THF with hexanal at 0 °C for 18h. [c] Reactions carried out in toluene with phenyl acetaldehyde at 0 °C for 1h. [d] Regioselectivity determined by ^{1}H NMR of the crude mixture. [e] *Syn/anti* ratio of the 1,2-adduct **8a** determined by ^{1}H NMR of the crude mixture. *Syn/anti* ratio of the 1,2-adduct **8b** determined by ^{1}H NMR and HPLC analysis of the crude mixture after acetylation (Ac_2O/Py). [f] Isolated yields after chromatographic purification on SiO_2. [g] Determined by HPLC on **8a** and **8b-Ac**. [h] Reaction time was 18 h.

Comparable results but lower ees were obtained with organocatalyst **L2**. After these preliminary results, our efforts concentrated on the α-alkylation of phenyl acetaldehyde as the obtained compound could be used for a novel asymmetric synthesis of blockbuster drug Ritalin (Scheme 1). To our delight, the alkylation reaction was very fast (1h at 0 °C) in a variety of solvents,[13] with the best results obtained in toluene using catalyst **L2**. A screening of Lewis acid showed a remarkable influence on the reaction outcome (entries 7-14). In particular, catalytic amounts of $Er(OTf)_3$ afforded compound **8b** with a good yield and a high regio- and stereoselectivity (entry 13). Racemic *threo*-methylphenidate hydrochloride (Ritalin) is a mild nervous system stimulant and the eutomer *(2R, 2'R)* is known to be 5 to 38 times more active than its enantiomer. Notwithstanding its clinical significance, to our knowledge, only one catalytic asymmetric synthesis has been so far described.[14] The optimized reaction conditions developed by us for an effective generation of 5,6-dihydropyridinium ion starting from pro-electrophile **7** afforded 1,2,5,6-tetrahydropyridine **8b-Ac** with an excellent

regioselectivity and a high stereoselectivity. After chromatographic purification, single diastereoisomer **8b-Ac**-*syn* (93 % ee) was easily converted into *threo (2R, 2'R)*-N-Boc-ritalinol **10**,[15] which is a known precursor to *threo-(2R, 2'R)* methylphenidate hydrochloride **11** (Scheme 1).[15,16]



Scheme 1. Short asymmetric formal synthesis of *threo*-methylphenidate.

To sum up, we have successfully developed mild, fast and highly enantioselective organocatalyzed α-alkylations of aldehydes with quinolinium and dihydropyridinium ions. The methodology uses easily available pro-electrophiles activated *in situ* with Lewis or Brønsted acids and allows the unprecedented syntheses of carbamoyl dihydroquinoline and tetrahydropyridine derivatives with introduction of chirality at the attacking carbon framework.

We acknowledge the financial support from the University of Pisa.

Notes and references

1 Review: Y. S. Lee, M. M. Alam, and R. S. Keri, *Chem. Asian J.,* 2013, **8**, 2906.

2 (a) J. Zhang, B. Tiwari, C. Xing, X. Chen, and Y. R. Chi, *Angew. Chem. Int. Ed.,* 2012, **51**, 3649; (*b*) L. Mengozzi, A. Gualandi, and P. G. Cozzi, *Chem. Sci.,* 2014, **5**, 3915; (*c*) A. Gualandi, L. Mengozzi, E. Manoni, and P. G. Cozzi, *Catal. Lett.,* 2015, **145**, 398.

3 For example see: I. Kumar, P. Ramaraju, N. A. Mir, D. Singh, V. K. Gupta, and Rajnikant, *Chem. Commun.,* 2013, **49**, 5645 and references cited therein.

4 For a very recent organocatalytic enantioselective alkenylation and arylation of N-carbamoyl tetrahydropyridines, see: X. Liu, Z. Meng, C. Li, H. Lou, and L. Liu, *Angew. Chem. Int. Ed*., 2015, **54**, 6012.

5 (a) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.,* 2004, **126**, 11808; (b) E. L. Myers, J. G. de Vries, and V. K. Aggarwal, *Angew. Chem. Int. Ed*., 2007, **46**, 1893; (c) Z. Sun, S. Yu, Z. Ding, and M. Da, *J. Am. Chem. Soc.,* 2007, **129**, 9300; (d) D. A. Black, R. E. Beveridge, and B. A. Arndtsen, *J. Org. Chem*., 2008, **73**, 1906; (e) M. A. Fernández-Ibáñez, B. Maciá, M. G. Pizzuti, A. J. Minnard, and B. L: Feringa, *Angew. Chem. Int. Ed*., 2009, **48**, 9339; (f) C. Nadeau, S. Aly, and K. Belyk, *J. Am. Chem. Soc.,* 2011, **133**, 2878; (g) S. T Chau, J. P. Lutz, K. Wu, and A. G. Doyle, *Angew. Chem. Int. Ed*., 2013, **52**, 9153; (h) S.-L Shi, X.F. Wei, Y. Shimizu, and M. Kanai, *J. Am. Chem. Soc.,* 2012, **134**, 17019; (i) M. Hussain, T. S.-L. Banchelin, H. Andersson, R. Olsson, and F. Almqvist, *Org. Lett.,* 2013, **15,** 54.

6 M. R. Monaco, P. Renzi, D. M. Scarpino Schietroma, and M. Bella, *Org. Lett.,* 2011, **13**, 4546.

7 Reviews: (*a*) A. E. Allen, and D. W. MacMillan, *Chem. Sci*., 2012, **3**, 633; (*b*) Z. Du, and Z. Shao, *Chem. Soc. Rev.,* 2013, **42**, 1337; (*c*) A. Gualandi, L. Mengozzi, C. M. Wilson, and P. G. Cozzi, *Chem. Asian. J.,* 2014, **9**, 984.

8 S. Crotti, F. Berti, and M. Pineschi, *Org. Lett.,* 2011, **13**, 5152.

9 In accordance with the literature, the TMS cleavage of the diarylprolinol silyl ether was not observed in these reaction conditions. See: M. H. Haindl, M. B. Schmid, K. Zeitler, and R. M. Gschwind, *RSC Adv.,* 2012, **2**, 5941.

10 The relative configuration of 1,2 adducts **3aa**-*syn* (major product) and **3aa**-*anti* (minor product) was initially assigned by ^{1}H and ^{13}C NMR after oxidation ($NaClO_2/H_2O_2$) to similar known carboxylic acid derivatives: A. Schmidt, D. Michalik, S. Rotzoll, E. Ullah, C. Fischer, H. Reinke, H. Görls, and P. Langer, *Org. Biomol. Chem*., 2008, **6**, 2804 (see ESI for details).

11 CCDC 1057075. An X-ray diffraction study on a single crystal of **5dc** led to the molecular structure shown in Figure 1. In the measurement, performed at room temperature, a certain degree of conformational disorder was present in the ethoxyl group. The conformation of the rest of the molecule is affected by the hydrogen interaction between O(3) and O(1), the O(3)···O(1) distance being 2.911(4) Å. The absolute configuration *R*,*R* of the chiral centers C(5) and C(13) was established on the basis of the Flack's parameter (0.017(11)).

12 For NMR study of the formation of prolinol ether enamine with propanal, see: M. B. Schmid, K. Zeitler, and R. M. Gschwind, *J. Am. Chem. Soc.,* 2011, **133**, 7065.

13 See ESI for details and expanded Table.

14 H. M. L. Davies, T. Hansen, D. W. Hopper, and S. A. Panaro, *J. Am. Chem. Soc.,* 1999, **121**, 6509.

15 The optical rotatory power for this compound was $[\alpha]_D^{20}$= +11.2 (c= 1.5, CH_2Cl_2) with respect to $[\alpha]_D^{20}$= +12.4 (c= 2.20, CH_2Cl_2) reported in: D. L. Thai, M. T. Sapko, C. T. Reiter, D. E. Bierer, and J. M. Perel, *J. Med. Chem*., 1998, **41**, 591.

16 M. Prashad, H.-Y., Kim, Y. Lu, Y. Liu, D. Har, O. Repic, T. J. Blacklock, and P. Giannousis, *J. Org. Chem.,* 1999, **64**, 1750.