Highly enantioselective nitroaldol reaction catalyzed by new chiral copper complexes†

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Remarkable generality in scope of DATs/Cu catalysts for enantioselective nitroaldol reaction is described; excellent levels of stereoinduction are recorded for a range of aldehydes (ee 81–99%, 17 examples) and the possibility to employ the present catalytic system as the key step for the preparation of highly functionalized tetrahydro-isoquinolines is demonstrated.

In recent years, considerable progress has been made in developing new catalytic and stereoselective processes addressing the synthesis of enantiomerically enriched building blocks.[1] Generality in scope, level of stereoinduction, use of readily available and cheap catalysts, mildness of reaction parameters and low loading of catalyst are some of the prominent issues usually taken into account to assess the suitability of catalytic systems for large scale productions.[2]

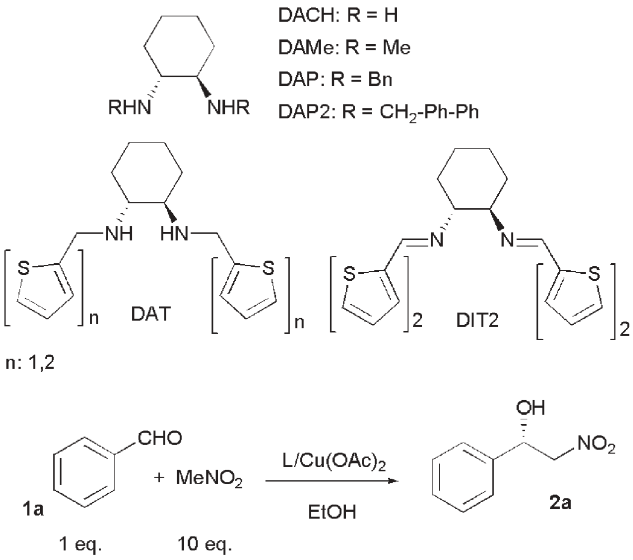
The nitroaldol (Henry) condensation[3] is a highly versatile carbon–carbon bond forming reaction, allowing a plethora of key molecular frameworks (β-hydroxynitroalkanes, 1,2-amino-alcohols and α-hydroxy carboxylic acids) to be synthesized in a straightforward manner.[4] Therefore, the development of practical catalytic asymmetric versions of this reaction is still largely desirable.[5]

Currently, chiral bifunctional coordination complexes have been described to control efficiently the stereochemical outcomes of this transformation (Shibasaki,[6a] Jørgensen,[6b] Trost,[6c] Yamada,[6d] Palomo[6e]). Despite the outstanding levels of enantiocontrol reached, these pioneering approaches have some limitations in the use of preformed silyl nitronates as nucleophiles, organic bases as additives, low reaction temperatures (often lower than −20 °C) or relatively high catalyst loadings.

Evans and coworkers have recently faced these issues by demonstrating the effectiveness of chiral weak Lewis acids ($Cu(OAc)_2$-bis-oxazoline complexes) in promoting a base-free nitroaldol condensation between nitromethane and a range of aldehydes.[7,8]

As a part of our research, toward the use of new versatile and fine-tunable C_2-symmetrical oligothiophene ligands[9] in asymmetric transformations, we explored the potentiality of bis-amino systems in the copper catalyzed condensation of nitromethane to the benzaldehyde (**1a**). From a survey of reaction parameters (Table 1) we were interested to find DAT1 and DAT2 superior to the bis-imino analogous (DIT2) for producing **2a** in 70% conversion within an 80 min reaction time (cat. 10 mol%). Moreover, although the length of the oligothienyl chain did not significantly affect the overall stereochemical outcome of the reaction (DAT1/2: ee = 89% and 91%, respectively), the role of the thienyl pendants was evident by considering the poor stereoselection obtained with less hindered DACH/DAMe ligands (entry 4–5, ee = 0–8%). Interestingly, attempts to also carry out the Henry reaction on **1a** with C_2-symmetrical bis-amino ligands bearing benzyl (DAP) and

Table 1 Optimization of reaction conditions for the enantioselective Henry reaction of **1a** and $MeNO_2$ promoted by chiral copper catalysts



Entry[a]	L (%)	*T*/°C	Time/h	Conv. (%)[b]	ee (%)[c]
1	DAT1 (12)	rt	1.2	70	89 (*S*)
2	DAT2 (12)	“	“	74	91 (*S*)
3	DIT2 (12)	“	“	77	17 (*R*)
4	DACH (12)	“	“	50	0
5	DAMe (12)	“	“	70	8 (*S*)
6	DAP (12)	“	“	56	51 (*S*)
7	DAP2 (12)	“	“	72	60 (*S*)
8	DAT2 (12)	0	16	99 (98)	96 (*S*)
9	DAT2 (6)	“	“	90	96 (*S*)
10	DAT2 (3)	“	“	78	96 (*S*)
11	DAT2 (1.2)	“	48	70	96 (*S*)
12	DAT2 (0.12)	rt	72	91 (72)[d]	84 (*S*)

[a] The reactions were carried out in EtOH with a Cu : L ratio 1 : 1.2. [b] Determined by HPLC and ^1H NMR. Isolated yields are given in brackets. [c] Determined by chiral HPLC (OD). The absolute configuration was assigned by comparison with the reported HPLC retention time. [d] The reaction was carried on a 10 mmol scale of **1a**.

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4-biphenyl (DAP2) pendants led to **2a** with significantly lower chemical/optical outcomes (conv.: 56%, 72% and ee 51%, 60%, respectively).

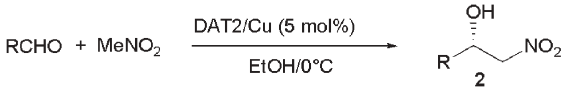
Lowering the reaction temperature to 0 °C led to an improvement in enantioselectivity (ee = 96%) with a persistent synthetically useful catalytic activity (98% yield, 16 h, entry 8). Finally, the effectiveness of the catalytic system was demonstrated in a gram-scale preparation (10 mmol of **1a**) by decreasing the loading of the catalyst to 0.1 mol%. Under these conditions, **2a** was obtained in >90% conversion and with still synthetically useful enantiomeric excess (84%) after 72 h (entry 12).‡ To the best of our knowledge, the S : C ratio of 1000 : 1 represents the lower catalytic loading applied to enantioselective Henry reactions to date.

To explore the generality of the method, we examined a variety of aldehydes including aromatic, aliphatic, heteroaromatic and α,β-unsaturated compounds (Table 2).

The presence of either electron-withdrawing and electron-donating substituents at various positions of the aromatic ring of aryl aldehydes was tolerated with ee ranging from 81% to 94% (entries 1–10, Table 2).

Moreover, it is worthy to note the level of stereoinduction recorded with both branched (**1m**, **1o**, ee = 97% and 93%, respectively) and more challenging no α branched aliphatic aldehydes (**1n**, **1q–p** ee up to 99%). In these cases, higher chemical and optical yields were achieved when the Henry reactions were carried out at rt (40 h), proving the presence of non-stereoselective pathways that become competitive at lowest temperatures.

Table 2 Proving the generality of the (*R*,*R*)-DAT2/Cu(OAc)$_2$ catalyzed enantioselective Henry reaction with a range of aldehydes (**1**)



1b: R = *p*MePh
1c: R = *p*ClPh
1d: R = *p*FPh
1e: R = *p*OMePh
1f: R = *o*OMePh
1g: R = *o*NO$_2$Ph
1h: R = *p*NO$_2$Ph
1i: R = C$_6$F$_5$
1j: R = 4PhPh
1k: R = 2-bithienyl
1l: R = PhCH=CH
1m: R = *t*Bu
1n: R = C$_7$H$_{15}$
1o: R = cyclohexyl
1p: R = Ph(CH$_2$)$_2$-
1q: R = BnOCH$_2$-

Entry^{a}	1	Time/h	*T*/°C	Yield (%)^{b}	ee (%)^{c}
1	**1b**	16	rt	75 (80)^{d}	90 (*S*)
2	**1c**	40	0	68 (79)	92 (*S*)
3	**1d**	“	“	71 (80)	94 (*S*)
4	**1e**	“	“	– (98)^{e}	94 (*S*)
5	**1f**	“	“	88 (95)	94 (*S*)
6	**1g**	“	“	92 (95)	94 (*S*)
7	**1h**	“	“	81 (98)	81 (*S*)
8	**1i**	“	“	62 (80)	90 (*S*)
9	**1j**	16	“	93 (99)	87 (*S*)
10	**1k**	40	“	42 (58)	88 (*R*)
11	**1l**	“	“	71 (78)	92 (*S*)
12	**1m**	“	rt	71 (90)	97 (*S*)
13	**1n**	“	“	78 (95)	99 (*S*)
14	**1o**	“	“	72 (98)	93 (*S*)
15	**1p**	“	“	53 (80)	87 (*S*)
16	**1q**	“	“	62 (85)	84 (*R*)

[a] The reactions were carried out in distilled EtOH at 0 °C with 5 mol% of copper (DAT2 : Cu(II), 1.2 : 1). [b] Conversions (^{1}H NMR) are given in brackets. [c] Determined by chiral HPLC (OD, AD, OJ, see ESI). The absolute configuration was assigned by comparison with the known optical rotation value and by analogy. [d] Progressive and spontaneous retro-Henry reaction was observed by storing the compound at rt. [e] Rapid decomposition of **2e** prevented an accurate purification. [f] 25% of dehydration compound was isolated.

In order to gain information on the nature of the pre-catalytic species, (±)-DAT2-Cu(OAc)$_2$ complex was easily isolated under mild conditions in 74% yield by condensing the ligand (racemic form) and the hydrate–copper salt in 1 : 1 ratio in EtOH.[10] Significant shifts of the IR bands for $\nu_{as}(CO^{2-})$ (18 cm^{-1}, 1584 cm^{-1}) and $\nu_s(CO^{2-})$ (39 cm^{-1}, 1421 cm^{-1}) toward lower energy were observed upon complexation respect to Cu(OAc)$_2$ in KBr (ν_{as} = 1602 cm^{-1}, ν_s = 1445 cm^{-1}).[10]

The blue complex yielded suitable crystals for X-ray diffraction studies (Fig. 1). Here, the expected distorted square planar geometry of the copper centre was observed with the non-bounded oxygen of the acetate groups occupying vacant apical coordination sites.[7] The two bithiophene arms are parallel to each other and oriented in opposite directions.

Encouraged by the versatility of our catalytic system, we performed the model Henry reaction (DAT2/Cu(OAc)$_2$ 5 mol%, 40 h, 0 °C) onto 3,5-dimethoxybenzaldehyde (**1r**) that is a valuable precursor for polycyclic alkaloids. In fact, enantiomerically enriched 2-aryl-ethylamines, bearing electron-rich aromatics, are key building blocks for the preparation of natural compounds (tetrahydro-isoquinolines and tetrahydro-β-carbolines)[11] through intramolecular aromatic alkylations (*i.e.* Pictet–Spengler condensation).[12]

Then, (*S*)-(+)-nitroalcohol **2r** (84% ee, Scheme 1) was reduced (H$_2$/Pd/C, balloon, 4 h) to leave the enantiomerically enriched amino-alcohol that was easily transformed to the *N*-FMOC-protected derivative (*S*)-**3r** (yield = 61% two steps, ee = 84%). Subsequent silylation of the hydroxy group and the removal of the *N*-Fmoc group (Me$_2$NH/THF) led to the desired 2-aryl ethylamine **5r** in 47% yield (two steps) without any loss of stereochemical information.

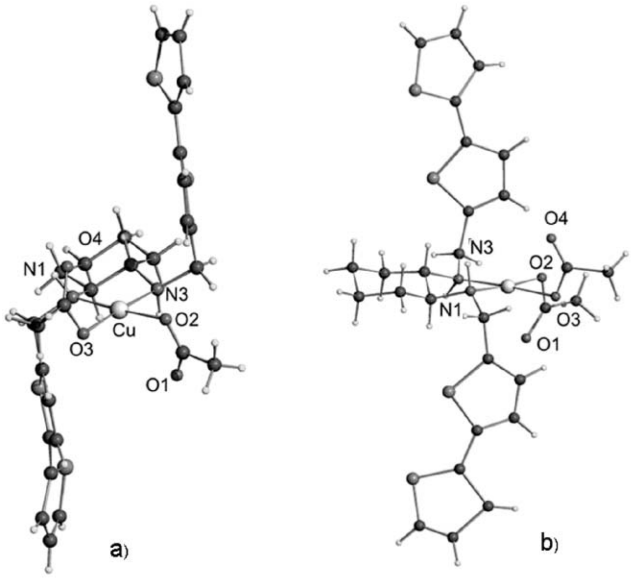
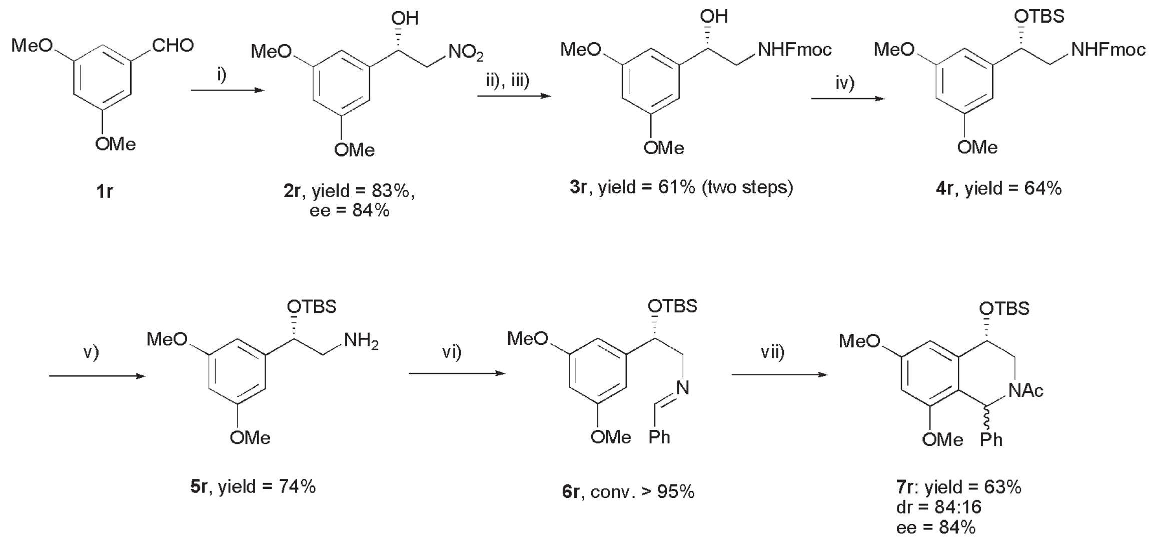


Fig. 1 Molecular structure of (±)-DAT2/Cu(OAc)$_2$. The (*S*,*S*)-enantiomer is shown; (a) front view; (b) side view. Selected bond lengths (Å): Cu(1)–O(3) 1.907(6), Cu(1)–O(2) 1.967(6), Cu(1)–N(1) 2.001(7), Cu(1)–N(2) 2.050(7), Cu(1)–O(4) 2.807(7), Cu(1)–O(1) 2.777(8).



Scheme 1 *Reagents and conditions*: (i) CH_3NO_2/DAT2/$Cu(OAc)_2$ (5 mol%), EtOH, 40 h, 0 °C; (ii) Pd/C, H_2, balloon, MeOH; (iii) FmocCl/TEA/DCM, rt, 16 h; (iv) TBSCl/Imid/DMF, rt, 16 h; (v) Me_2NH/THF, rt, 30 min; (vi) PhCHO/$MgSO_4$/CH_2Cl_2/rt/16 h; (vii) AcCl/lut/CH_3CN/0 °C/16 h.

Finally, through the preformed imine **6r**, the targeted tetra-hydro-isoquinoline **7r** was obtained in good yield (63%) and 84% ee (5.3 : 1 diastereoisomeric ratio) by following a metallo-free variant of a known Pictet–Spengler procedure (AcCl, lutidine, CH_3CN, 0 °C).[13]

In conclusion, we have presented a new class of valuable chiral copper–diamine promoting agents for highly enantioselective Henry reaction. Generality in scope (aliphatic, aromatic, hetero-aromatic, α,β-unsaturated aldehydes: ee up to 99%) and mildness of reaction conditions (up to 0.1% catalyst loading) locate the present catalytic system among the most efficient procedures for the synthesis of enantiomerically enriched nitroalcohols and functionalized polycyclic aromatic compounds.§

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Notes and references

‡ *Representative asymmetric Henry reaction* (Table 1, entry 9): A flamed two necked-bottom 50 mL flask was charged with 5.6 mg (0.012 mmol) of (*R*,*R*)-DAT2 and 1.9 mg (0.01 mmol) of [$Cu(OAc)_2 \cdot nH_2O$] and the solids were stirred under vacuum until a blue powder is obtained (*ca.* 1.5 h). Then, 15 mL of anhydrous EtOH were added followed by 1.0 mL of **1a** (10 mmol). The solution was stirred for 10 min then 5.86 mL of $MeNO_2$ (100 mmol) were added. The mixture was then stirred at rt for 72 h and the volatiles removed under reduced pressure. An aliquot was analyzed by ^1H NMR to determine the reaction conversion (91%). The green crude was then purified through a short pad of silica (*n*-hex : AcOEt 9 : 1) and pure (*S*)-**2a** was obtained as a pale yellow viscous oil in 72% yield (1.20 g), ee = 84%.

§ *Synthesis of (±)-DAT2-Cu(OAc)$_2$*: A 50 mL round-bottom flask containing a stirring bar was charged with dry EtOH (8 mL), (±)-DAT2 (150 mg, 0.32 mmol) and [$Cu(OAc)_2 \cdot n(H_2O)$] (60 mg, 0.32 mmol). The resulting blue solution was stirred at rt overnight, then the solvent was evaporated under reduced pressure. The crude product obtained was washed with dry Et_2O (5 mL), and the pale blue solid was collected by filtration and dried under vacuum. Yield = 76% (144 mg); mp 190 °C (decomposition); IR (KBr): = 3448(br), 3129(s), 3066(m), 2937(s), 2859(w), 1584(s), 1382(s), 837(m) cm^{-1}; suitable crystals for X-ray analysis were obtained by slow diffusion (CH_2Cl_2/*n*-hex, 7 days, rt). CCDC 299401. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613019d.

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