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Enantioselective aza-Henry reactions of cyclic α-carbonyl ketimines under bifunctional catalysis†

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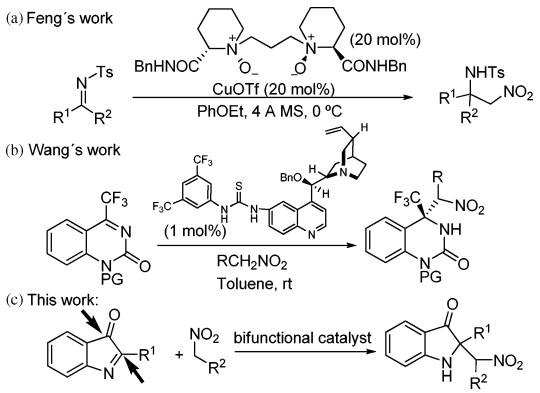
The aza-Henry reaction of nitroalkanes with the C═N group of 2-aryl-3*H*-indol-3-ones catalyzed by thiourea-chincona derivatives takes place with good yield and high ee's.

The aza-Henry reaction[1] represents one the most useful and efficient methodologies for preparing chiral amines. Moreover, the resulting nitroamines can be used as intermediates for the synthesis of 1,2-diamines[2] and other moieties present in important pharmaceutical and biological products.[3] Therefore, a number of new approaches towards the catalytic asymmetric aza-Henry reaction have been reported over the last decade. Excellent results have been described in the seminal works of Shibasaki *et al.*[4] and Jørgensen *et al.*[5] using aldimines as electrophiles,[6] which were further improved by other authors working with metal catalysts[6a,b] and also with aldimines under bifunctional catalysis.[6c–g] However, the reactions with the less reactive ketimines, which give access to the more challenging *t*-alkyl amines,[7] are much less satisfactory and, to our knowledge, only two examples involving catalytic asymmetric aza-Henry reactions of ketimines have been reported. Feng *et al.* described the reactions of sulfonylketimines catalyzed by chiral *N,N′*-dioxide-copper(I) complexes, with moderate to excellent enantioselectivity, but rather low yields (eqn (a), Scheme 1),[8] whereas, more recently, Wang *et al.*[9] reported the first organocatalytic protocol for performing the addition of nitroalkanes to highly reactive trifluoromethyl ketimines under thiourea catalysis (eqn (b), Scheme 1). Unfortunately, this method could not be extended beyond trifluoromethyl ketimines to other less reactive derivatives. These precedents indicate that the catalytic enantioselective aza-Henry reaction remains unsolved.

Indol-3-ones bearing a chiral quaternary center at the 2-position are important skeletons because they are present in the structure of several natural products, such as pseudoindoxyl alkaloids (Fig. 1), and in pharmaceutical agents.[10] They have also been used as intermediates in the synthesis of natural products such as hinckdentine A[11] (Fig. 1). Consequently, the search for



Scheme 1 Two different approaches for the aza-Henry reaction with ketimines and the present work.

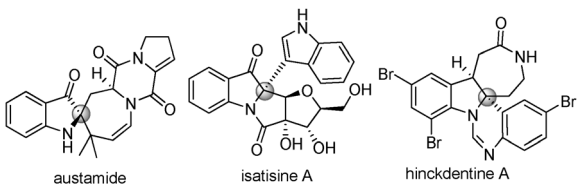


Fig. 1 Natural products with 2,2-disubstituted indolin-3-one moieties.

new protocols for the enantioselective synthesis of these indol-3-ones is also important.[12] At this point, we reasoned that the addition of nitroalkanes to indolone derivatives (eqn (c), Scheme 1) could be interesting as an example of aza-Henry reactions of ketimines to provide 2,2-disubstituted indol-3-ones. In this work we present the results obtained in the addition of nitroalkanes to 2-aryl-3*H*-indol-3-ones under bifunctional catalysis for obtaining enantiomerically enriched indolin-3-ones bearing a chiral quaternary centre at the 2-position.

As the main problem observed in the use of ketimines as electrophiles derives from the low reactivity of the C═N, we chose the indolone derivatives shown in Scheme 1 as our substrates because of the double activation conferred by the carbonyl group on the C═N. These two groups are connected and coplanar, thus maximizing their mutual electronic influences (I and M effects). On the other hand, bifunctional catalysis was chosen to simultaneously govern the approach of the reagent to the planar substrate. However, the presence of two electrophilic functional groups in the same ring

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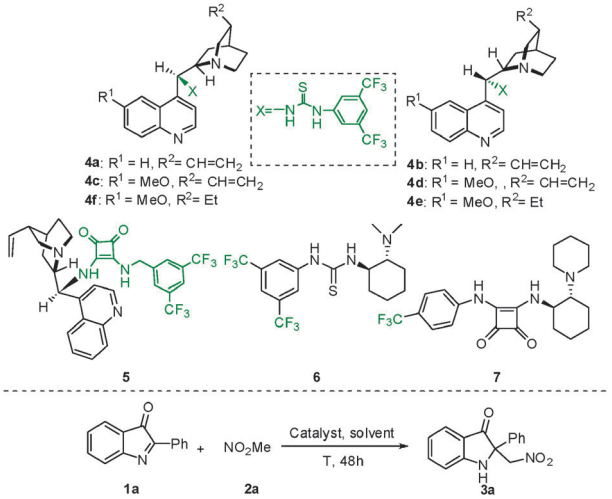
Table 1 Screening of various reaction conditions[a]



Entry	Cat (10 mol%)	Solvent	T (°C)	Conversion (%)	er
1	**4a**	CH_2Cl_2	Rt	60	23 : 77
2	**4b**	CH_2Cl_2	Rt	>99	90 : 10
3	**4c**	CH_2Cl_2	Rt	70	21 : 79
4	**4d**	CH_2Cl_2	Rt	>99	89 : 11
5	**4e**	CH_2Cl_2	Rt	>99	92 : 8
6	DABCO	CH_2Cl_2	Rt	30	—
7	**5**	CH_2Cl_2	Rt	10	24 : 76
8	**6**	CH_2Cl_2	Rt	50	87 : 13
9	**7**	CH_2Cl_2	Rt	10	25 : 75
10	**4e**	CH_2Cl_2	0	40	91 : 9
11	**4e**	CH_2Cl_2	−20	10	90 : 10
12[b]	**4e**	CH_2Cl_2	Rt	>99	89 : 11
13	**4e**	$CHCl_3$	Rt	10	77 : 23
14	**4e**	Toluene	Rt	>99	92 : 8
15	**4e**	***p*-Xylene**	**Rt**	**>99**	**95 : 5**
16[c]	**4e**	*p*-Xylene/DCM[d]	0	20	90 : 10
17[c]	**4e**	*o*-Xylene	Rt	15	92 : 8
18[c]	**4e**	C_6F_6	Rt	15	67 : 33
19[c]	**4e**	TBME	Rt	20	82 : 18
20[c]	**4e**	DCE	Rt	60	92 : 8
21	**4f**	*p*-Xylene	Rt	<5	—

[a] All the reactions were performed on a 0.064 mmol scale in 0.24 mL of the indicated solvent and 10 equiv. of nitromethane. [b] A 1.0 M concentration was used. [c] 24 h reaction time. [d] A 5 : 1 mixture was used.

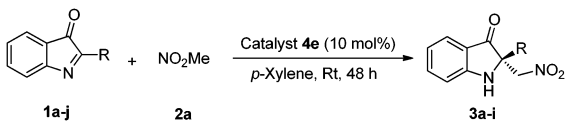
could generate chemoselectivity problems (C=N[13] *versus* C=O[14] addition).

The addition of nitromethane **2a** to 2-phenyl-3*H*-indol-3-one **1a** was used as a model reaction for optimization (Table 1). A series of thioureas[15] and squaramides[16] (entries 1–9) were tested at different temperatures (10–12) and solvents (13–20). The use of the alkaloid thiourea **4a** in CH_2Cl_2 at rt gave **3a** as the only product in 60% conversion after 48 h, indicating a completely chemoselective reaction (attack on the C=O was not detected in the reaction mixture). However, **3a** was obtained in a rather low enantiomeric ratio (23 : 77, entry 1, Table 1). Using **4b**, higher conversion (>99%) and better er (90 : 10) were obtained (entry 2, Table 1). Thioureas **4c–d** (entries 3 and 4, Table 1) and Takemoto's catalyst **6** (entry 8, Table 1) showed lower enantiomeric ratios, and squaramides, **5** (entry 7, Table 1) and **7** (entry 9, Table 1), decreased the conversion to 10% (no catalytic activity). The monofunctional catalyst DABCO also gave poor conversion (entry 6). The best results were achieved with catalyst **4e**, derived from hydroquinine-thiourea (entry 5), which provided complete conversion in 48 h at rt (er = 92 : 8). Stereoselectivity was not improved by decreasing the reaction temperature (entries 10 and 11) nor by increasing the solvent concentration (entry 12). Finally, we studied the influence of solvent (entries 13–20), obtaining the best results, full conversion and 95 : 5 er with *p*-xylene (entry 15). Unfortunately, the reaction with the *pseudo*-enantiomer catalyst **4f** gave only poor conversion (entry 21).

With these optimized conditions in hand, we then tested the scope of this reaction (Table 2). When the reaction was scaled up to 1.0 mmol, neither the yields nor the stereoselectivities were significantly affected (compare entries 1 and 2). The study of a variety of 2-aryl-3*H*-indol-3-ones revealed that this reaction was similarly efficient for aryl residues containing electron-donating and electron-withdrawing groups (entries 3–8). The 2-naphthyl (**1h**) (entry 9) and the biphenyl derivatives (**1i**) were also tolerated, though the latter group gave worse conversion (entry 10). A Boc-protected indol (**1j**) is also compatible, providing **3j** with good yield and moderate enantioselectivity (entry 11).

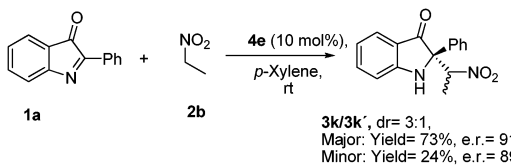
Next, we focused our attention on nitroderivatives different to nitromethane (Scheme 2), yielding compounds with two chiral centers. Reactivity of nitroethane was similar, affording a 3:1 diastereomeric mixture **3k**/**3k′**, presumably differing in the configuration at the carbon joined to the nitrogen, with both epimers exhibiting er values similar to that observed in the examples shown in Table 2. As a control experiment, the major

Table 2 Scope of various 2-aryl-3*H*-indol-3-ones[a]



Entry	R	Product	Yield (%)	er
1	Ph-**1a**	**3a**	90	95 : 5
2[b]	Ph-**1a**	**3a**	85	93 : 7
3	*p*-Me–C_6H_4-**1b**	**3b**	93	91 : 9
4	*p*-Et–C_6H_4-**1c**	**3c**	93	92 : 8
5	*p*-MeO–C_6H_4-**1d**	**3d**	95	85 : 15
6	*p*-F–C_6H_4-**1e**	**3e**	93	91 : 9
7	*p*-Cl–C_6H_4-**1f**	**3f**	81	93 : 7
8	*o*-Br–C_6H_4-**1g**	**3g**	81	98 : 2
9	2-Naphthyl-**1h**	**3h**	>99	92 : 8
10	*p*-C_6H_4-Ph-**1i**	**3i**	37	92 : 8
11	 **1j**	**3j**	52	80 : 20

[a] All reactions were performed on a 0.2 mmol scale in 0.72 mL of dry *p*-xylene using 10 equiv. of nitromethane. [b] Reaction was carried out on a 1.0 mmol scale.



Scheme 2 Reaction with nitroethane.

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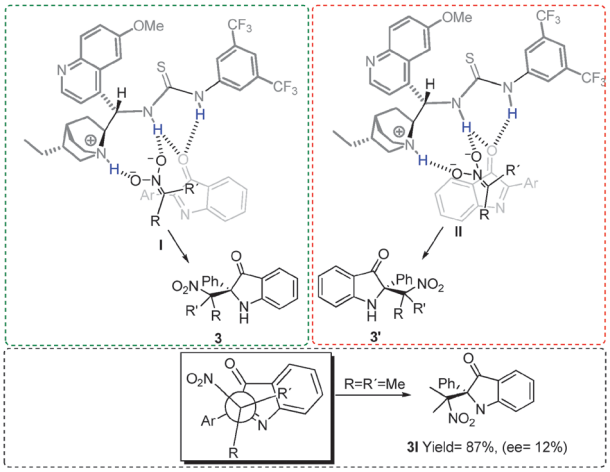

Scheme 3 Stereochemical proposal.

diastereoisomer **3k** was placed under the same reaction conditions with catalyst **4e** (10 mol%). A mixture of diastereoisomers **3k**/**3k′** (3 : 1) was obtained, indicating the easy epimerization of the obtained product by the basic catalyst.

We were able to obtain proper crystals for X-ray analysis in the case of compound **3g**,† which allowed us to unequivocally assign its absolute configuration as *S* (see ESI†). This assignment was then used for the remainder of the compounds **3** depicted in Table 2. The stereochemical proposal is outlined in Scheme 3. The carbonyl oxygen at the 2-aryl-3*H*-indol-3-one **1** can be doubly associated to the thiourea catalyst **4e** through hydrogen bonds. Simultaneously, the nitronate (generated by deprotonation of nitromethane at the quinuclidine core) will also be associated to the catalyst. Starting from this preorganized superstructure, the nucleophilic attack can take place on the pro-*S* (approach I) and the pro-*R* (approach II) faces of the associated indoline **1**, respectively, yielding isomers **3** and **3′** (Scheme 3). The stronger stereoelectronic interactions of the nitronate with the indoline in approach II (nitronate is over the indolone system which is not in approach I) would explain the observed enantioselectivity, with enantiomers **3** being predominant in reactions with nitromethane. A similar situation is observed in reactions with nitroethane, yielding a mixture of diastereoisomers (the α-proton with respect to the NO_2 group is easily epimerizable), with both exhibiting similar er values to that observed in Table 2. The Newman projection for approach I (bottom, Scheme 3) suggests that its stability would not be strongly affected when R is not hydrogen (as with R = Me and R′ = H, see Scheme 2), thus maintaining a similar enantioselectivity to nitromethane. However, the stability of I would be substantially decreased when R′ is not hydrogen. In order to confirm this hypothesis, we carried out the reaction of the indolone **1** with 2-nitropropane (R = R′ = Me) (bottom, Scheme 3). Interestingly, the reaction gave the expected product **3l**, but the enantioselectivity was strongly decreased (12% ee). The reversibility of this reaction was proved by isolation of **3l** and was placed with catalyst **4e** and nitromethane. Non incorporation of nitromethane or alteration of product **3l** was detected, indicating that reversibility under these conditions cannot occur.

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Notes and references

1 For a recent review, see: E. Marqués-López, P. Merino, T. Tejero and R. P. Herrera, *Eur. J. Org. Chem.*, 2009, 2401.
2 For a review, see: D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580.
3 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001.
4 (*a*) K. Yamada, S. J. Harwood, H. Gröger and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1999, **38**, 3504; (*b*) K. Yamada, G. Moll and M. Shibasaki, *Synlett*, 2001, 980; (*c*) N. Tsuritani, K. Yamada, N. Yoshikawa and M. Shibasaki, *Chem. Lett.*, 2002, 276; (*d*) S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 4900; (*e*) Z. Chen, H. Morimoto, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 2170.
5 (*a*) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2001, **123**, 5843; (*b*) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2992; (*c*) K. R. Knudsen and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 1362.
6 (*a*) For selected examples, see: B. M. Trost and D. W. Lupton, *Org. Lett.*, 2007, **9**, 2023(*b*) H. Zhou, D. Peng, B. Qin, Z. R. Hou, X. H. Liu and X. M. Feng, *J. Org. Chem.*, 2007, **72**, 10302; (*c*) For leading references in organocatalytic aza-Henry reaction with aldimines, see: T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625(*d*) B. M. Nugent, R. A. Yoder and J. N. Johnston, *J. Am. Chem. Soc.*, 2004, **126**, 3128; (*e*) T. Yoon and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 466; (*f*) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci and V. Sgarzani, *Tetrahedron*, 2006, 375; (*g*) C. M. Bode, A. Ting and S. E. Schaus, *Tetrahedron*, 2006, 11499.
7 For a review of chiral quaternary centers, see: Bella and T. Gasperi, *Synthesis*, 2009, 1583 and references cited therein.
8 C. Tan, X. Liu, L. Wang, J. Wang and X. Feng, *Org. Lett.*, 2008, **10**, 5305.
9 H. Xie, Y. Zhang, S. Zhang, X. Chen and W. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 11773.
10 For selected examples, see: (*a*) A. Asai, S. Nagamura, E. Kobajashi, K. Gomi and H. Saito, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1215; (*b*) H. Takayama, M. Kurihara, S. Subhadhirasakul, M. Kitajima, N. Aimi and S. Sakai, *Heterocycles*, 1996, **42**, 87 and references cited therein.
11 (*a*) A. J. Blackman, T. W. Hambly, K. Picker, W. C. Taylor and N. Thirasasana, *Tetrahedron Lett.*, 1987, **28**, 5561. For synthesis of 8-desbromohinckentine A, see: (*b*) Y. Liu and W. W. McWhorter Jr, *J. Am. Chem. Soc.*, 2003, **125**, 4240 and references cited therein.
12 (*a*) For other approaches to the synthesis of quaternary centers of indolone derivatives, for racemic versions, see: A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354(*b*) J.-M. Adam and T. Winkler, *Helv. Chim. Acta*, 1984, **67**, 2186; (*c*) K.-Q. Ling, *Chin. J. Chem.*, 1996, **14**, 265. See also ref. 13; (*d*) For asymmetric versions, see; (*e*) M. Rueping, S. Raja and A. Nuñez, *Adv. Synth. Catal.*, 2011, **353**, 563; (*f*) L. Li, M. Han, M. Xiao and Z. Xie, *Synlett*, 2011, 1727; (*g*) Q. Yin and S.-L. You, *Chem. Sci.*, 2011, **3**, 1344.
13 (*a*) C. Berti, L. Greci and L. Marchetti, *J. Chem. Soc., Perkin Trans. 2*, 1979, 233; (*b*) G. Tommasi, P. Bruni, L. Greci, P. Sgarabotto and L. Righi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 681; (*c*) C. Berti, G. Corrado, M. Lucedio and L. Marchetti, *Gazz. Chim. Ital.*, 1975, **105**, 993.
14 For a competitive reaction with Grignard reagents in the C=N and C=O addition, see: Y. Liu and W. W. McWhorter, *J. Org. Chem.*, 2003, **68**, 2618.
15 (*a*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*b*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744.
16 (*a*) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem.–Eur. J.*, 2011, **17**, 6890; (*b*) R. Ian Storer, C. Aciro and L. H. Jones, *Chem. Soc. Rev.*, 2011, **40**, 2330.