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Proline-Catalyzed Asymmetric Formal α-Alkylation of Aldehydes via Vinylogous Iminium Ion Intermediates Generated from Arylsulfonyl Indoles**

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Catalysis with chiral secondary amines (asymmetric aminocatalysis) has become a well-established and powerful synthetic tool for modern synthetic chemistry.[1] The impressive level of scientific competition and high quality research generated in this area have opened up new synthetic opportunities that were considered inaccessible only a few years ago. Even reactions that had been considered impossible became a reality through aminocatalysis. One of the best validations of this approach is the development of the catalytic, asymmetric direct α-alkylation of aldehydes.[2] This highly challenging and valuable C–C bond-forming strategy[3] was completely unknown before the advent of asymmetric aminocatalysis.[4] In 2004, Vignola and List presented the first catalytic asymmetric intramolecular α-alkylation of haloaldehydes under enamine catalysis.[5] They demonstrated the ability of proline-derived catalysts to overcome the classical drawbacks associated with the stoichiometric alkylation of preformed aldehyde enolates, such as the tendency toward aldol condensation and the Canizzaro or Tischenko reactions.[6] However, extension of their aminocatalytic strategy to an intermolecular version failed because of deactivation of the amine catalyst by N-alkylation with the alkyl halide.[5a]

Thus, chemists started to search for different aminocatalytic strategies to accomplish the challenging goal of an intermolecular formal aldehyde α-alkylation.[7] In 2006, Ibrahem and Córdova reported a non-asymmetric catalytic intermolecular α-allylic alkylation of aldehydes by combination of transition-metal and enamine catalysis.[8] More recently, MacMillan and co-workers exploited a new aminocatalytic activation concept, based on radical intermediates, to solve the synthetic problems of the catalytic asymmetric α-allylation,[9a] arylation,[9a] enolation,[9b] and vinylation[9c] of unmodified aldehydes.

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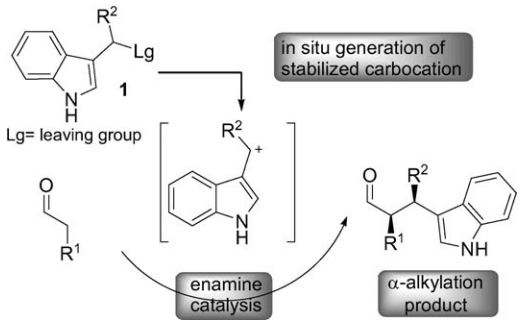
Herein, we report a new challenging strategy for the asymmetric intermolecular enamine-catalyzed formal α-alkylation of aldehydes.[2] The novel approach is founded upon the use of a reagent **1** (Scheme 1), which, because of the presence



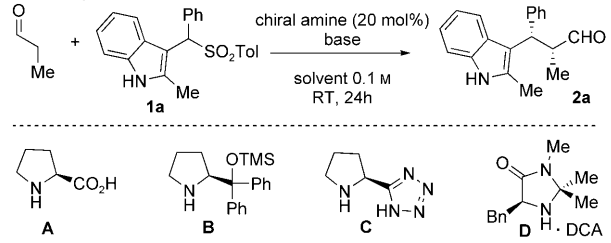
Scheme 1. New approach for the intermolecular α-alkylation of aldehydes.

of a suitable leaving group, can generate a highly stabilized carbocation that can readily intercept the enamine intermediate.[10] L-Proline, a natural molecule that has played a central role in the development of asymmetric aminocatalysis,[11] proved to be the best catalyst for affording valuable alkylation products with an indolic core in good yield and with high level of stereoselectivity.

At the outset of our investigations, we identified the nature of the alkylating agent **1** as the crucial point for the development of an efficient formal alkylation strategy. Recently, we introduced 3-(1-arylsulfonylalkyl)indoles as suitable electrophilic precursors.[12] The sulfonyl moiety at the benzylic position of 3-substituted indoles constitutes a good leaving group, which under basic or acidic conditions allows the generation of an electrophilic species that is able to react with nucleophiles. With this in mind, and convinced of the compatibility between a chiral secondary amine and a stronger base, necessary for the in situ generation of the actual alkylating intermediate, we sought to develop a simple protocol for the aminocatalytic formal alkylation of aldehydes. For the exploratory studies, we selected the reaction between propanal and the bench-stable sulfonylindole **1a**, leading to the 3-substituted indole **2a** with two adjacent stereocenters (Table 1).

Initial results revealed that, of the bases tested, whether organic or inorganic, only KF supported on basic alumina was able to promote the in situ formation of the electrophilic compound from **1a**. Surprisingly, in such a heterogeneous

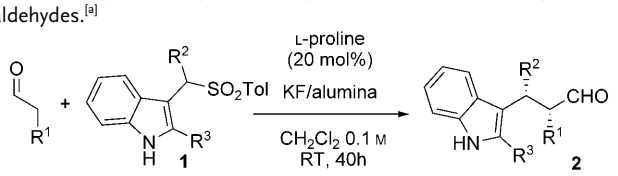
Table 1: Optimization studies.[a]



Entry	Cat.	Base	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**A**	K_2CO_3	CH_2Cl_2	0	–	–
2	**A**	DBU	CH_2Cl_2	< 5	–	–
3	**A**	KF/alumina[e]	CH_2Cl_2	51	3:1	86
4	**B–D**	KF/alumina[e]	CH_2Cl_2	< 5	–	–
5	**A**	KF/alumina[e]	toluene	45	2.5:1	74
6	**A**	KF/alumina[e]	$CHCl_3$	63	3:1	75
7	**A**	KF/alumina[e]	THF	< 10	–	–
8	**A**	KF/alumina[e]	acetone	0	–	–
9	**A**	KF/alumina[f]	CH_2Cl_2	86	5:1	90

[a] Reactions carried out on a 0.1 mmol scale using 3 equiv of propanal; DCA = dichloroacetic acid; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis. [e] 80 mg per 0.1 mmol. [f] 40 mg per 0.1 mmol.

Table 2: Scope of the proline-catalyzed intermolecular α-alkylation of aldehydes.[a]



Entry	R^1	R^2	R^3	**2**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	Ph	Me	**a**	86	5:1	90
2	Et	Ph	Me	**b**	92	6.5:1	86
3	*i*Pr	Ph	Me	**c**	79	8:1	90
4	$PhCH_2$	Ph	Me	**d**	74	6:1	89
5	$MeSCH_2$	Ph	Me	**e**	77	4.5:1	88
6	allyl	Ph	Me	**f**	75	5:1	88
7	*i*Pr	*p*-Br-C_6H_4	Me	**g**	80	12:1	92
8	*i*Pr	*p*-MeO-C_6H_4	Me	**h**	82	7:1	84
9	*i*Pr	*p*-Me-C_6H_4	Me	**i**	78	7:1	88
10	*i*Pr	Ph	Ph	**j**	77	3:1	88
11	*i*Pr	Ph	H	**k**	80	3:1	11
12	Me	pentyl	Ph	**l**	63	1.5:1	75

[a] Reactions carried out on a 0.2 mmol scale using 3 equiv of aldehydes and 80 mg of KF on alumina. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] Determined by chiral HPLC analysis.

system only L-proline provided catalytic activity, leading to the formation of **2a** in good yield and reasonable stereoselectivity (Table 1, entry 3). All the other chiral secondary amines tested (**B**–**D**) failed in promoting the reaction (Table 1, entry 4), highlighting the crucial function of the carboxylic group of **A**. We also found a trend toward increased rates and stereoselectivity as the polarity of the solvent decreased (Table 1, entries 5–8). The best result in terms of both yield and stereocontrol was achieved by performing the proline-catalyzed reaction in CH_2Cl_2 and adjusting the amount of the KF on alumina (Table 1, entry 9). These catalytic conditions were selected for further exploration aimed at expanding the scope of this transformation.

As portrayed in Table 2, the method proved to be successful for a wide range of aliphatic aldehyde substituents, including alkenyl and heterosubstituted groups (entries 1–6, d.r. > 4.5:1, 86–90% *ee*).

Using isovaleraldehyde, structural variation in the alkylating reagent **1** was then briefly inspected (Table 2, entries 7–11). Whereas the presence of different substituents R^2 on the aryl group had apparently little influence on the stereochemical outcome of the reaction (Table 2, entries 7–9), the steric nature of the indole core had a direct effect on the stereoselectivity (Table 2, entries 10 and 11): that is, the lack of a 2-substituent on the indolic scaffold drastically lowered the stereoselectivity (Table 2, entry 11).[13] Finally, also sulfonyl indole with an aliphatic R^2 substituent can be employed, although the α-alkylation product **2l** was isolated with moderate stereoselectivity (d.r. 1.5:1, 75% *ee*; Table 2, entry 12).

The relative and absolute configuration of compound **2d** was determined to be 2*R*,3*S* by anomalous dispersion X-ray crystallography of the corresponding tosylated alcohol **3**, obtained by simple aldehyde reduction (Figure 1).[14]

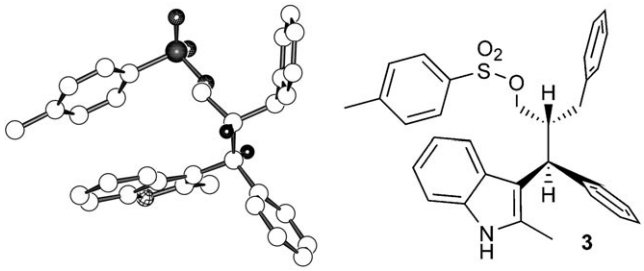
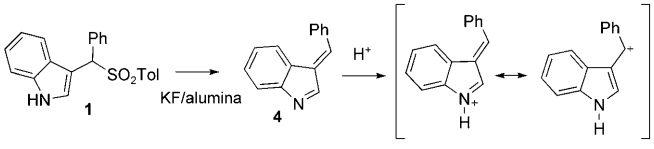


Figure 1. X-ray crystal structure of compound **3**.

At this point of our investigations, a detailed mechanistic explanation of the stereodifferentiation appears premature. However, all the experimental evidence supports the direct involvement of the carboxylic group of proline.[15]

Although rationalization of the catalytic system is complicated by the presence of a heterogeneous basic support, a crucial role of the acid may be envisaged when considering the likely formation of intermediate **4** after deprotonation and loss of the leaving group of **1** (Scheme 2). Protonation of this vinylogous imino derivative **4** by the carboxylic group of the catalyst would strongly activate the system toward a nucleophilic attack, resembling iminium ion activation.[16] However, formation of the carbocation, which would preserve the aromaticity of the indolic core, and its involvement



Scheme 2.

in the C–C bond-forming event may also be envisaged.[10,17] Within this mechanistic framework, the derived proline anionic enamine species might engage in electrostatic association through the pendant carboxylate group with the positively charged intermediate.[18] This hypothesis is consistent with the lack of reactivity of the secondary amines **B**–**D** tested and the deleterious effect of polar reaction media on both reactivity and stereoselectivity.[19]

In summary, we have discovered a novel strategy for the enamine-catalyzed formal α-alkylation of aldehydes. The use of L-proline allows easy access to relevant 3-indolyl derivatives **2** with high diastereo- and enantiocontrol, affording an easy alternative to the classical Friedel–Crafts route to these compounds.[20] Further studies are focusing on the extension of the method and on complete comprehension of the mechanism involved. [21]

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[1] For recent reviews on aminocatalysis, see: a) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; d) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79.

[2] The conventional α-alkylation of carbonyl compounds is considered to be an S_N2 addition to alkyl halides and generally utilizes stoichiometric amounts of metal enolates.

[3] a) *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**; b) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem.* **2005**, *117*, 2282; *Angew. Chem. Int. Ed.* **2005**, *44*, 2242.

[4] For phase-transfer catalytic asymmetric α-alkylation of glycine derivatives, see: a) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222 and references therein. For catalytic asymmetric alkylations of preformed lithium enolates with oligoamine catalysts, see: b) M. Imai, A. Hagihara, H. Kawasaki, K. Manabe, K. Koga, *J. Am. Chem. Soc.* **1994**, *116*, 8829. For metal-catalyzed asymmetric alkylations of preformed tin enolates, see: c) A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 62.

[5] a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450; b) A. Fu, B. List, W. Thiel, *J. Org. Chem.* **2006**, *71*, 320. This reaction was the first nucleophilic substitution proceeding under enamine catalysis and opened up unexplored routes for asymmetric aminocatalysis.

[6] a) H. O. House, W. C. Liang, P. D. Weeks, *J. Org. Chem.* **1974**, *39*, 3102; b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 8829.

[7] For organocatalytic asymmetric domino reactions consisting of Michael addition followed by intramolecular α-alkylation of aldehydes, leading to cyclic compounds, see: a) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; b) R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028; c) R. Rios, J. Vesely, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835; d) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, 120, 7649; *Angew. Chem. Int. Ed.* **2008**, 47, 7539.

[8] I. Ibrahem, A. Córdova, *Angew. Chem.* **2006**, *118*, 1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1952.

[9] a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004; c) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398.

[10] Both the carbocation and the vinylogous iminium ion intermediate depicted in Scheme 2 are contributing resonance structures. One referee suggested that the presented process be considered as a "simple" conjugate addition, in which the catalytically generated enamine intercepts the vinylogous iminium ion intermediate. However, an S_N1-type reaction involving the carbocation, leading to a "formal" α-alkylation, may also be possible (see Ref. [17]). Considering the unconventional nature of the electrophilic system, the presented process surely escapes classical definitions.

[11] For reviews, see: a) B. List, *Tetrahedron* **2002**, *58*, 5573; b) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904.

[12] a) R. Ballini, A. Palmieri, M. Petrini, R. R. Shaikh, *Adv. Synth. Catal.* **2008**, *350*, 129; b) A. Palmieri, M. Petrini, *J. Org. Chem.* **2007**, *72*, 1863; c) R. Ballini, A. Palmieri, M. Petrini, E. Torregiani, *Org. Lett.* **2006**, *8*, 4093.

[13] Also the use of 5-chloro-(2*H*)-sulfonyl indole derivative afforded poor results in terms of stereoselectivity (88% yield, d.r. 3:1, 17% *ee*). This result is likely due to a steric rather than an electronic effect.

[14] CCDC 700758 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] O-Methylation of the carboxylic group of proline had a deleterious effect on both the reactivity and selectivity of the process (25 mol% of hydrochloric salt of proline methyl ester, less than 30% conversion, d.r. 1.1:1 and <10% *ee* under the optimal reaction conditions).

[16] Adding silica gel (100 mg per 0.1 mmol) to the reaction mixture had a beneficial effect on the reactivity, which supports the mechanistic requirement for the protonation of **4**. Even catalysts that proved to be inactive under the reported conditions led to product formation: for example, catalyst **B** (25 mol%) in the reaction of propanal with **1a** afforded **2a** in 45% yield with high enantioselectivity (85% *ee*) but poor diastereoselectivity (d.r.1.1:1).

[17] The formation of such a carbocation has been recently proposed by Enders; see: a) D. Enders, A. A. Narine, F. Toulgoat, T. Bisschops, *Angew. Chem.* **2008**, *120*, 5744; *Angew. Chem. Int. Ed.* **2008**, *47*, 5661. For related papers, see: b) F. Colombo, G. Cravotto, G. Palmisano, A. Penoni, M. Sisti, *Eur. J. Org. Chem.* **2008**, 2801; c) B. Ke, Y. Qin, Q. He, Z. Huang, F. Wang, *Tetrahedron Lett.* **2005**, *46*, 1751.

[18] The proposed mechanism closely resembles the direct electrostatic activation (DEA) concept advanced by MacMillan to rationalize the mechanism of the aminocatalytic asymmetric cyclopropanation of enals; see: a) R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3240. It should be also noted that proline is typically a poor catalyst for enamine-activated aldehyde additions to Michael acceptors: b) B. List, P. Pojarliev, J. Martin, *Org. Lett.* **2001**, *3*, 2423..

[19] The sense of asymmetric induction is opposite to that observed in other proline-catalyzed asymmetric α-functionalization of aldehydes believed to proceed by a hydrogen-bond-directing approach of the electrophiles. The observed stereochemical outcome is consistent with the proposed electrostatic activation mode when assuming the *syn-E*-enamine of proline as the reactive intermediate, because of the closer proximity with the vinylogous iminium ion intermediate; see Ref. [18a] for similar

considerations. Theoretical studies are underway to shed more light on the mechanistic path.

[20] A stereoselective Friedel–Crafts approach to **2** should be based upon an asymmetric addition to α,β-disubstituted unsaturated aldehydes, a challenging yet elusive transformation. For a different organocatalytic entry to **2**, see: Y. Chi, S. T. Scroggins, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2008**, *130*, 6322.

[21] Note added in proof: After acceptance of this manuscript, the asymmetric intermolecular α-alkylation of aldehydes with activated alkyl halides has been accomplished, exploiting the combination of photoredox catalysis with emamine catalysis: D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, DOI:10.1126/science.1161976.

