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Copper Complex of Aminoisoborneol Schiff Base Cu_2(SBAIB-d)$_2$: An Efficient Catalyst for Direct Catalytic Asymmetric Nitroaldol (Henry) Reaction

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Abstract: A new bifunctional copper complex of the aminoisoborneol Schiff base – Cu_2(SBAIB-d)$_2$ – has been developed for the effective direct catalytic asymmetric Henry reaction. One mol% of this catalyst produces the expected Henry products in high yields (up to 99%) with excellent enantioselectivities (up to 98% *ee*). The utility of the present catalyst was also extended to the Henry reaction with nitroethane and 1-nitropropane that furnished the corresponding products in moderate to high yields (up to 99%) with moderate to high enantioselectivities of *syn* (up to 98% *ee*) and *anti* (up to 98% *ee*) diastereomers. The highlights of this catalytic system are easy manipulation, air and moisture tolerance, the need for 1 mol% of an easily synthesizable catalyst and the high enantioselectivities achieved for a wide range of substrates.

Keywords: asymmetric catalysis; copper(II) complexes; enantioselectivity; Henry reaction; Schiff bases

Introduction

The direct nitroaldol (Henry) reaction is one of the most renowned C–C bond formation reactions in the organic synthesis. The resultant bifunctional β-hydroxynitroalkane product is a highly versatile synthon for the synthesis of numerous functionally varying compounds such as 1,2-amino alcohols, α-hydroxy ketones, α-amino ketones, α-hydroxycarboxylic acid and various pharmaceuticals.[1] Since Shibasaki's asymmetric variant of this reaction,[2] numerous efforts have been devoted to the development of a catalytic asymmetric Henry reaction by various metal catalysts including copper,[3] zinc,[4] chromium,[5] cobalt,[6] bimetal catalysts,[7] rare-earth metals,[8] with structurally varying chiral ligands, organocatalysts[9] as well as by biocatalysts.[10] In terms of chiral ligands, Shibasaki's BINOL complex,[2] Evans' BOX complex,[3b] Pedro's *N*,*N*-ligand (especially aminopyridine),[1d] Lan's bisimidazoline,[3q] Wan's bissulfonamide-diamine,[3r] Wang's recently reported tertiary amino alcohol,[3u] and Trost's dinuclear zinc-amino alcohol[4a] are some of the most successful ligands for the Henry reaction. Although salen and Schiff base ligands are considered as one of the most privileged ligands in asymmetric synthesis,[11] their applications in the Henry reaction have not attracted considerable attention because of the formation of nitroaldol products in moderate to good *ee*. Figure 1 shows the structures of various salen and Schiff base ligands and their metal complexes used in the Henry reaction.

Among Wang's β-amino alcohol Schiff base-Cu complexes **1**–**4**,[12a,c] the 2.5 mol% of complex **4**[12c] showed moderate to good *ee* in EtOH. Pedro's *N*,*N*-ligands Schiff bases,[3i] and iminopyridines **5** and **6** were the most promising ligand with $Cu(OAc)_2 \cdot 2H_2O$ at −65 °C using 11 mol%, however, only a maximum of 85% chiral induction was achieved. The bisthiophene Schiff base **7** was reported to give a mere 17% *ee* in this reaction.[3j] The Cu(I) complex of phosphine-Schiff base ligand **8** also yielded the corresponding product with only 80% *ee*.[12b] Other Schiff bases **9**,[12d] **11**,[12e] and **12**[12g] were found to be inefficient ligands for the Henry reaction. Although the recently reported chiral Cu(II) complex of paracyclopane Schiff base **10** has shown good *ee*,[12f] its substrate scope was limited only to 2-nitrobenzaldehye. Interestingly, amino or diamino compounds, formed by reduction of these Schiff bases, became excellent catalysts for the Henry reaction; for example, Pedro's *N*,*N*-diamine (amino-

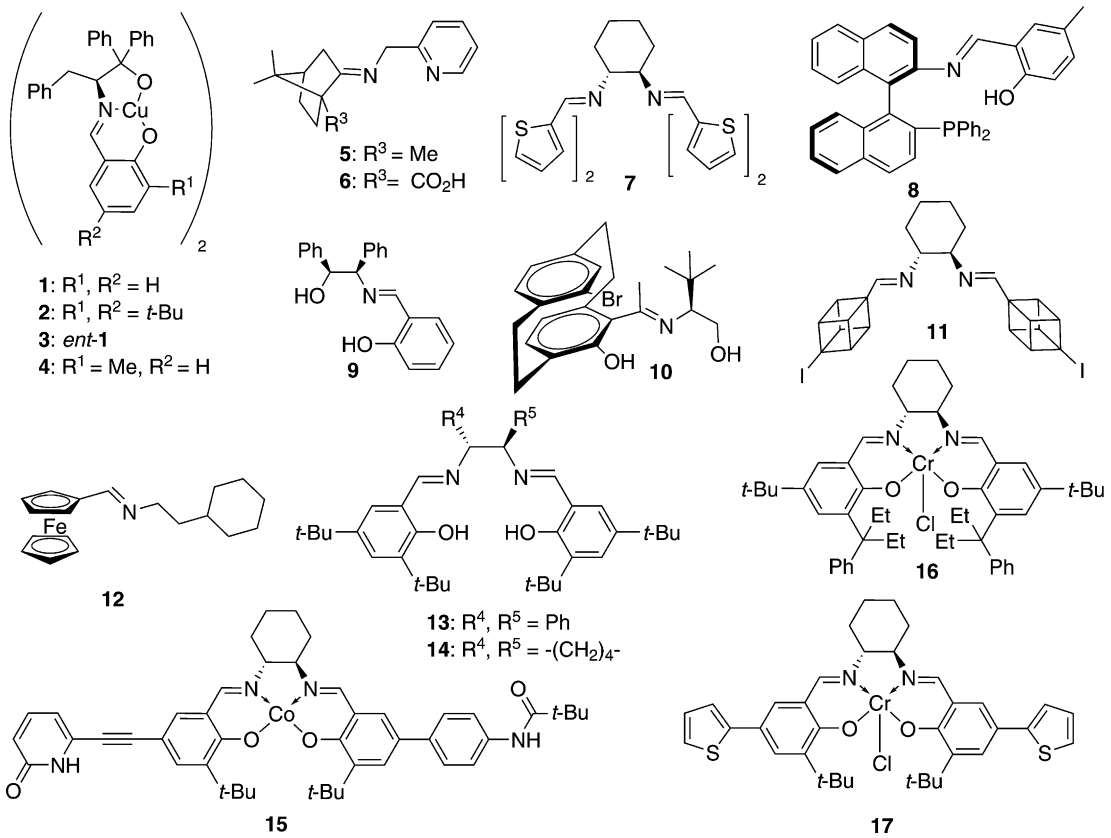


Figure 1. The structure of Schiff bases, salen ligands and its metal complexes used in the asymmetric Henry reaction.

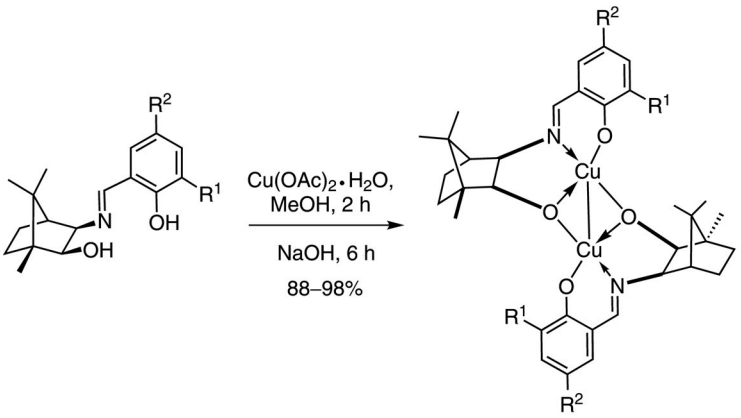
pyridine) ligand[1d] and the recently reported[3u] tridentate proline alcohol ligand. Compared to Schiff bases, various metal complexes (Co,[6] Cr,[5] Cu[3g,7b]) of salen ligands **13**–**17** showed enhanced chiral induction; however, they did have limitations such as absence of a strong chiral induction for *m*- and *p*-substituted benzaldehydes, demand for an inert atmosphere, and a low reaction temperature. The development of highly efficient and simple asymmetric catalysts is one of our goals.[13] With our present state of understanding, we envisioned that the bifunctional copper complex of Schiff bases of aminoisoborneol [Cu_2(SBAIB)$_2$] (Scheme 1) would overcome this prolonged inefficiency of Schiff base ligands for the Henry reaction. The strong steric hindrance in the *exo*-aminoisoborneol backbone is considered to play a pivotal role for high chiral induction, in contrast to most of the reported β-amino alcohol Schiff bases that do not possess such a huge steric hindrance when forming metal complexes.

Although many catalytic systems have been developed for the Henry reaction, many still have drawbacks such as the need of high catalyst loading, low reaction temperature, inert atmosphere to achieve high enantioselectivity, and, the limitation in the substrate scope of aldehydes as well as nitroalkanes other than nitromethane. Therefore, always finding a new catalyst results in breakthrough in prolonged failures and circumvents the limitations. Herein, this study describes a practically very simple, highly efficient asymmetric Henry reaction by using bifunctional Cu_2(SBAIB)$_2$ for numerous aldehydes and nitroalkanes.

Results and Discussion

Preparation of Copper Complex Cu_2(SBAIB)$_2$

Considering the wide application of copper metal in the Henry reaction, we synthesized seven copper complexes **18**–**24** from camphor-based ligands. The Schiff bases of aminoisoborneol [SBAIB] **18a**–**24a** were prepared as shown in Scheme 1. These (+)-SBAIB ligands can be prepared easily from (1*R*)-camphor in high yields, among these (+)-SBAIB-a **18a** showed a good to excellent chiral induction in the asymmetric phenylacetylene addition reaction to various aldehydes.[13c] The proposed structure of these complexes was verified by the X-ray crystal structure of Cu_2[(+)-SBAIB-d]$_2$ **21** (Figure 2).



18a: (+)-SBAIB-a: R^1 = H, R^2 = H
19a: (+)-SBAIB-b: R^1 = *t*-Bu, R^2 = *t*-Bu
20a: (+)-SBAIB-c: R^1 = Me, R^2 = Me
21a: (+)-SBAIB-d: R^1 = Me, R^2 = H
22a: (+)-SBAIB-e: R^1 = H, R^2 = Me
23a: (+)-SBAIB-f: R^1 = *t*-Bu, R^2 = H
24a: (+)-SBAIB-g: R^1 = H, R^2 = *t*-Bu

18: Cu_2[(+)-SBAIB-a]$_2$: R^1 = H, R^2 = H
19: Cu_2[(+)-SBAIB-b]$_2$: R^1= *t*-Bu, R^2 = *t*-Bu
20: Cu_2[(+)-SBAIB-c]$_2$: R^1= Me, R^2 = Me
21: Cu_2[(+)-SBAIB-d]$_2$: R^1= Me, R^2 = H
22: Cu_2[(+)-SBAIB-e]$_2$: R^1= H, R^2 = Me
23: Cu_2[(+)-SBAIB-f]$_2$: R^1= *t*-Bu, R^2 = H
24: Cu_2[(+)-SBAIB-g]$_2$: R^1= H, R^2 = *t*-Bu

Scheme 1. Synthesis of copper complex of Schiff base ligands (SBAIB).

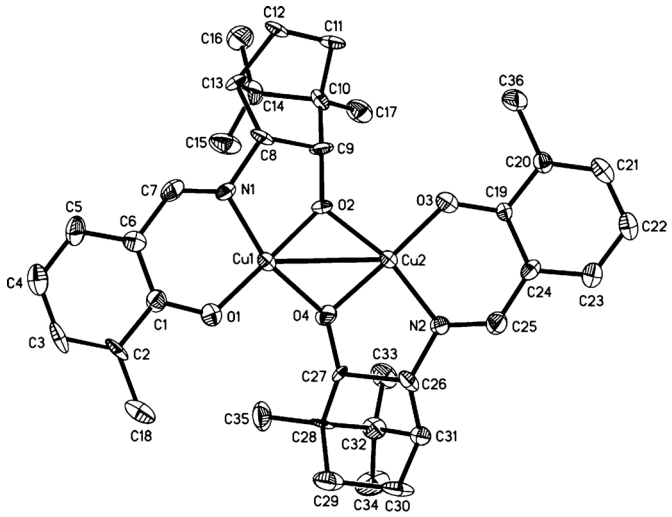


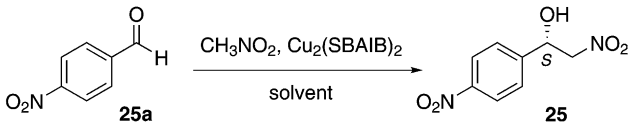
Figure 2. X-ray crystal structure of Cu_2(SBAIB-d)$_2$, **21** [CCDC 865431; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif].

Optimization of the Reaction Conditions

With the seven Cu complexes **18**–**24** in hand, the optimization of the Henry reaction was started with 4-nitrobenzaldehyde **25a** and nitromethane in ethanol with 2.5 mol% of the Cu complex. Cu_2(SBAIB-d)$_2$ **21** was found to be the best catalyst among the seven Cu complexes (Table 1, entries 1–7). The reaction was carried out by addition of aldehyde **25a** to the 3 h pre-stirred mixture of Cu complex and nitromethane in ethanol at room temperature under atmospheric conditions. Various solvents were screened for this reaction with 2.5 mol% **21** (Table 1, entries 8–14). Among these solvents *tert*-butyl alcohol emerged as a promising solvent resulting in high yield (97%) and *ee* (86%) in 36 h reaction time. Then the higher mol% of catalyst **21** was tested and we found that there was no improvement for yield and *ee* of 2-nitro-1-(4-nitrophenyl)ethanol **25** (Table 1, entries 15–17). An immediate addition of aldehyde to the catalytic system has only afforded a lower yield and *ee* (Table 1, entry 18) in 36 h. When the amount of $MeNO_2$ was increased to 20 volumes (with respect to aldehyde **25a**) with *t*-BuOH (20 volumes), a higher *ee* (91%) with the yield of 97% was obtained (Table 1, entry 21), conversely, when it was decreased from 10 equivalents, lower *ee*s were observed (Table 1, entries 19 and 20). To enhance the enantioselectivity, the 20:20 volume ratio of $MeNO_2$ and *t*-BuOH was changed into 10:30, 30:10, and 40:0. However, the results (Table 1, entries 22–24) showed lower *ee* compared to the 20:20 solvent volume ratio result.

The mol% of ligand **21** was decreased to study any amplification in *ee* (Table 1, entries 25 and 26). As expected, both 1 mol% as well as 0.5 mol% **21** yielded the best results (93% *ee*), better than any of the earlier conditions with ligand **21**, however, the reaction time for the latter was long (Table 1 entry 26). Then the reaction temperature was optimized, a lower *ee* was resulted for both higher and lower temperatures (Table 1, 27 and 28). Finally the total volume of the reaction solvent (40 volumes) was decreased to 20 volumes (10:10 $MeNO_2$/*t*-BuOH) (Table 1, entry 29), also the reaction with the achiral base additive triethylamine (5 mol%) (Table 1, entry 30) was studied,

Table 1. Catalyst screening and optimization.[a]



Entry	Ligand [mol%]	$MeNO_2$ [equiv.][b]	Solvent [vol][c]	Temp. [°C]	Time [h]	Yield [%][d]	*ee* [%][e]
1	**18** (2.5)	10	EtOH (40)	r.t.	36	99	13
2	**19** (2.5)	10	EtOH (40)	r.t.	36	99	16
3	**20** (2.5)	10	EtOH (40)	r.t.	36	34	51
4	**21** (2.5)	10	EtOH (40)	r.t.	36	48	62
5	**22** (2.5)	10	EtOH (40)	rt	36	28	38
6	**23** (2.5)	10	EtOH (40)	r.t.	36	72	41
7	**24** (2.5)	10	EtOH (40)	r.t.	36	43	45
8	**21** (2.5)	10	MeOH (40)	r.t.	36	50	33
9	**21** (2.5)	10	*i*-PrOH (40)	r.t.	36	86	82
10	**21** (2.5)	10	*t*-BuOH (40)	r.t.	36	97	86
11	**21** (2.5)	10	THF (40)	r.t.	42	21	68
12	**21** (2.5)	10	DCM (40)	r.t.	42	27	54
13	**21** (2.5)	10	ACN (40)	r.t.	42	trace	NA
14	**21** (2.5)	10	DMF (40)	r.t.	42	trace	NA
15	**21** (5)	10	*t*-BuOH (40)	r.t.	36	50	78
16	**21** (10)	10	*t*-BuOH (40)	r.t.	36	74	71
17	**21** (20)	10	*t*-BuOH (40)	r.t.	36	83	81
18	**21** (2.5)[f]	10	*t*-BuOH (40)	r.t.	36	80	81
19	**21** (2.5)	1.5	*t*-BuOH (40)	r.t.	36	10	80
20	**21** (2.5)	5	*t*-BuOH (40)	r.t.	36	50	78
21	**21** (2.5)	20 (vol)	*t*-BuOH (20)	r.t.	42	98	91
22	**21** (2.5)	10 (vol)	*t*-BuOH (30)	r.t.	40	98	87
23	**21** (2.5)	30 (vol)	*t*-BuOH (10)	r.t.	40	88	90
24	**21** (2.5)	40 (vol)	nil	r.t.	40	37	79
25	**21 (1)**	20 (vol)	*t*-BuOH (20)	r.t.	40	>99	93
26	**21** (0.5)	20 (vol)	*t*-BuOH (20)	r.t.	60	97	93
27	**21** (1)	20 (vol)	*t*-BuOH (20)	40	30	98	90
28	**21** (1)	20 (vol)	*t*-BuOH (20)	10	76	57	91
29	**21** (1)	10 (vol)	*t*-BuOH (10)	r.t.	40	96	91
30	**21** (1)[g]	20 (vol)	*t*-BuOH (20)	r.t.	3	99	2

[a] All the reactions were carried out in an 8-mL vial with 50 mg of **25a** (1 equiv.) under atmospheric air.
[b] $MeNO_2$ used as purchased without further drying.
[c] All the solvents were used as purchased without further drying.
[d] Yield refers to the chromatographically pure compounds.
[e] The *ee* was determined by chiral HPLC on Chiralcel OD-H column.
[f] Aldehyde was added immediately to **21** in *t*BuOH/$MeNO_2$.
[g] 5 mol% triethylamine was used as additive.

but the results were not promising, especially with triethylamine a mere 2% *ee* was obtained for the corresponding product despite the very short (3 h) reaction time.

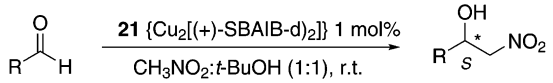
Therefore, entry 25 (>99% yield and 93% *ee*) in Table 1 was chosen as an the optimized conditions and are as follows: an addition of aldehyde **25a** to the pre-stirred solution of catalyst Cu_2[(+)-SBAIB-d]$_2$ **21** (1 mol%) in 40 volumes of solvent (20:20 $MeNO_2$/*t*-BuOH) at room temperature under atmospheric conditions.

Enantioselective Henry Reaction of Various Aldehydes

The scope of the ligand was then explored under the optimized condition. The results are shown in Table 2. Numerous aldehydes were screened, which enabled preparation of the corresponding β-nitro alcohols in excellent yield (up to 99%) with very high enantioselectivity (up to 98%).

The electron-withdrawing and electron-donating substituents on aromatic aldehydes had a significant effect on the reaction rate; generally, the former had

Table 2. Enantioselective Henry reaction of nitromethane with various aldehydes.

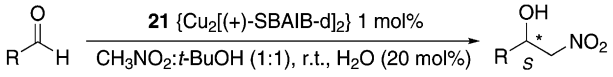


Entry	R[a]	Product	Time [h]	Yield [%][b]	*ee* [%][c]	Sign/Conf.[d]
1	4-$NO_2C_6H_4$ **25a**	**25**	40	99	93	+/*S*
2	3-$NO_2C_6H_4$ **26a**	**26**	38	94	91	+/*S*
3	2-$NO_2C_6H_4$ **27a**	**27**	37	99	97	–/*S*
4	4-$CH_3C_6H_4$ **28a**	**28**	96	83	92	+/*S*
5	3-$CH_3C_6H_4$ **29a**	**29**	96	86	94	+/*S*
6	2-$CH_3C_6H_4$ **30a**	**30**	80	96	92	+/*S*
7	4-$CH_3OC_6H_4$ **31a**	**31**	96	85	93	+/*S*
8	3-$CH_3OC_6H_4$ **32a**	**32**	96	89	93	+/*S*
9	2-$CH_3OC_6H_4$ **33a**	**33**	85	96	93	+/*S*
10	4-FC_6H_4 **34a**	**34**	90	96	95	+/*S*
11	3-FC_6H_4 **35a**	**35**	96	93	95	+/NA
12	2-FC_6H_4 **36a**	**36**	90	98	97	+/*S*
13	4-ClC_6H_4 **37a**	**37**	96	91	94	+/*S*
14	3-ClC_6H_4 **38a**	**38**	96	84	96	+/*S*
15	2-ClC_6H_4 **39a**	**39**	86	97	98	+/*S*
16	4-BrC_6H_4 **40a**	**40**	96	93	90	+/*S*
17	3-BrC_6H_4 **41a**	**41**	96	90	94	+/*S*
18	2-BrC_6H_4 **42a**	**42**	84	98	98	+/*S*
19	4-CNC_6H_4 **43a**	**43**	69	96	91	+/*S*
20	3-CNC_6H_4 **44a**	**44**	69	88	91	+/NA
21	4-$EtOCOC_6H_4$ **45a**	**45**	96	93	91	+/NA
22	Ph **46a**	**46**	96	90	91	+/*S*
23	4-*t*-BuC_6H_4 **47a**	**47**	96	91	92	+/*S*
24	4-PhC_6H_4 **48a**	**48**	96	89	89	+/*S*
25	2-PhC_6H_4 **49a**	**49**	86	96	90	+/NA
26	4-$BnOC_6H_4$ **50a**	**50**	96	52	89	+/NA
27	3,5-$(CH_3O)_2C_6H_3$ **51a**	**51**	96	76	88	+/*S*
28	2-naphthyl **52a**	**52**	96	86	92	+/*S*
29	1-naphthyl **53a**	**53**	96	88	96	+/*S*
30	furfuryl **54a**	**54**	96	69	93	+/*S*
31	2-thiophenyl **55a**	**55**	100	56	92	+/*S*
32	*E*-cinnamyl **56a**	**56**	96	72	88	+/*S*
33	α-Me-*E*-cinnamyl **57a**	**57**	96	42	90	–/*S*
34	Me_2CHCH_2 **58a**	**58**	96	88	81	–/*S*
35	cyclohexyl **59a**	**59**	96	65	83	+/*S*
36	$PhCH_2$ **60a**	**60**	96	86	77	–/*S*
37	$PhCH_2CH_2$ **61a**	**61**	96	96	96	–/*S*
38	*n*-heptyl **62a**	**62**	96	91	82	+/*S*
39	*n*-decyl **63a**	**63**	96	86	76	+/*S*

[a] All the reactions were carried out in an 8-mL vial with 50 mg of aldehyde (1 equiv.) with 1 mol% **21**.
[b] Yield refers to the chromatographically pure compounds.
[c] The *ee* was determined by chiral HPLC on various chiral columns, see the Supporting Information for more details.
[d] The absolute configuration of the products was determined on the basis of sign of specific rotation and its peaks order in the chiral HPLC.

a higher reaction rate for this catalytic system. *ortho*-Substituted aromatic aldehydes exhibited a slightly higher enantioselectivity compared to *meta*- and *para*-substituted benzaldehydes (Table 2, entries 3, 12, 15, and 18). New substrates for the Henry reaction such as 3-fluoro- (**35a**), 3-cyano- (**44a**), 3-ethoxycarbonyl- (**45a**), 2-phenyl- (**49a**) and 4-benzyloxybenzaldehyde (**50a**) also yielded the corresponding Henry products in high enantioselectivity (Table 2, entries 11, 20, 21, 25, and 26, respectively) with high yields except for 4-benzyloxybenzaldehyde (**50a**), which showed a moderate yield in 96 h. The polycyclic aromatic aldehydes (1- and 2-naphthaldehydes, Table 2, entries 28 and 29) also yielded highly enantioenriched products. Gratifyingly, the heteroaromatic aldehydes, furfural (**54a**) and 2-thiophenecarboxaldehyde (**55a**), also showed

Table 3. Enantioselective Henry reaction with 20 mol% water.



Entry	Aldehyde[a]	Product	Time [h]	Yield [%][b,d]	*ee* [%][c,d]	Sign/Conf.[e]
1	**25a**	**25**	40	96 (99)	92 (93)	+/*S*
2	**26a**	**26**	38	95 (94)	91 (91)	+/*S*
3	**27a**	**27**	38	99 (99)	96 (97)	−/*S*

[a] The reactions were carried out with aldehydes (0.33 mmol), **21** (0.0033 mol, 1 mol%) and H_2O (0.066 mmol, 20 mol%).
[b] Yield refers to the chromatographically pure compounds.
[c] The *ee* was determined by chiral HPLC on Chiralcel OD-H column.
[d] The values in brackets are the results of the Henry reactions without water (Table 2, entries 1, 2, and 3).
[e] The absolute configuration of the products was determined on the basis of sign of specific rotation and its peaks order in the chiral HPLC.

very high chiral inductions with moderate yields (Table 2, entries 30, and 31). Although the yields were moderate to good for α,β-unsaturated aldehydes (Table 2, entries 32, and 33), they displayed good enantioselectivity in their products. We were delighted to find good to excellent enantioselectivities and yields for various unbranched and branched aliphatic aldehydes (Table 2, entries 34–39). As the best result for aliphatic aldehydes, the Henry product **61** (96% yield and 96% *ee*) was obtained for 3-phenylpropionaldehyde **61a** (Table 2, entry 37). All the Henry products synthesized using catalyst **21** possess the *S* configuration as compared with the literature.

Although the optimized conditions for this reaction used commercially available *t*-BuOH without further drying, to test the effect of water, studies were conducted with 20 mol% of water. Interestingly, the obtained results were considerably promising (Table 3). The effect of water is significantly low as the enantioselectivity and yield of the corresponding products remained almost same as for products obtained without water. This became credible evidence that the current catalytic system is tolerable for moisture, is practically very simple, and can be achieved without any precaution for exclusion of moisture.

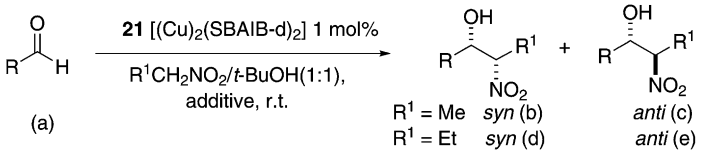
Nitroaldol (Henry) Reaction with Other Nitroalkanes

The scope of the nitroaldol (Henry) reaction with nitroalkanes other than nitromethane remains limited for many catalytic systems in the literature. Therefore, the feasibility of this catalytic system for other nitroalkanes was studied. When the optimized conditions were used for nitroethane, yields in the range of low to moderate with low diastereoselectivity and moderate *ee* were obtained in 120 h (Table 4, entries 1–4). However, *ortho*-nitrobenzaldehyde (**27a**) showed high *ee* for both *syn* **27b** (96%) and *anti* **27c** (96%) diastereomers in moderate yield (62%) with moderate *de* for *anti* (66:34). Achiral additives (bases and phenols) have been known to influence the yield, *ee*, and *de* in the Henry reaction.[14] We initially carried out the reaction with various achiral bases as additives (not shown), nevertheless, none of them yielded a promising result. Therefore, we then screened several phenolic additives for the reaction between nitroethane and either *p*- and *m*-nitrobenzaldehyde (**25a** and **26a**, respectively) (Table 4, entries 5–9). Although no enhancement in *de* occurred, we were pleased to find a good yield (92%) and *ee* (*syn* **25b**/*anti* **25c**; 80/93) for the aldehyde **25a** with 10 mol% of 4-methoxyphenol [4-$MeOC_6H_4OH$] as an additive (Table 4, entry 9). However, when applying 10 mol% 4-$MeOC_6H_4OH$ to the reaction of a slightly electron-rich aldehyde, 2-methylbenzaldehyde (**30a**), (Table 4, entry 10), the diastereomeric mixture *syn* **30b**/*anti* **30c** was obtained in only a moderate yield (60%) with moderate *ee* (*syn*/*anti*; 89:80). To amplify the yield and *ee*, various mole amounts of 4-$MeOC_6H_4OH$ were screened (Table 4, entries 11–14). Consequently, 50 mol% 4-$MeOC_6H_4OH$ afforded the Henry product in an excellent yield (99%) with excellent *ee* of *syn* **30b** (94%) and *anti* **30c** (91%) (Table 4, entry 12).

Under these optimized conditions then various aldehydes were explored (Table 4, entries 15–21). Yields and *ee*s were in the range of good to excellent; however, for the 2-fluorobenzaldehyde product **36b**/**36c** (Table 4, entry 19) only a moderate yield (51%) was obtained. As a best result 98% *ee* was obtained for *syn* diastereomer **33b** of the 2-methoxybenzaldehyde product. For the *anti* isomer, both 2-methyl- (**30a**) and 2-bromobenzaldehyde (**42a**) yielded the best result (91% *ee*).

Thereafter, when 10 mol% benzoic acid [$PhCO_2H$] was used as an achiral additive, a superior *ee* was determined for aldehyde **30a** (Table 4, entry 22) compared to 4-$MeOC_6H_4OH$ (50 mol%). A series of alde-

Table 4. Henry reaction with nitroethane and 1-nitropropane.[a]



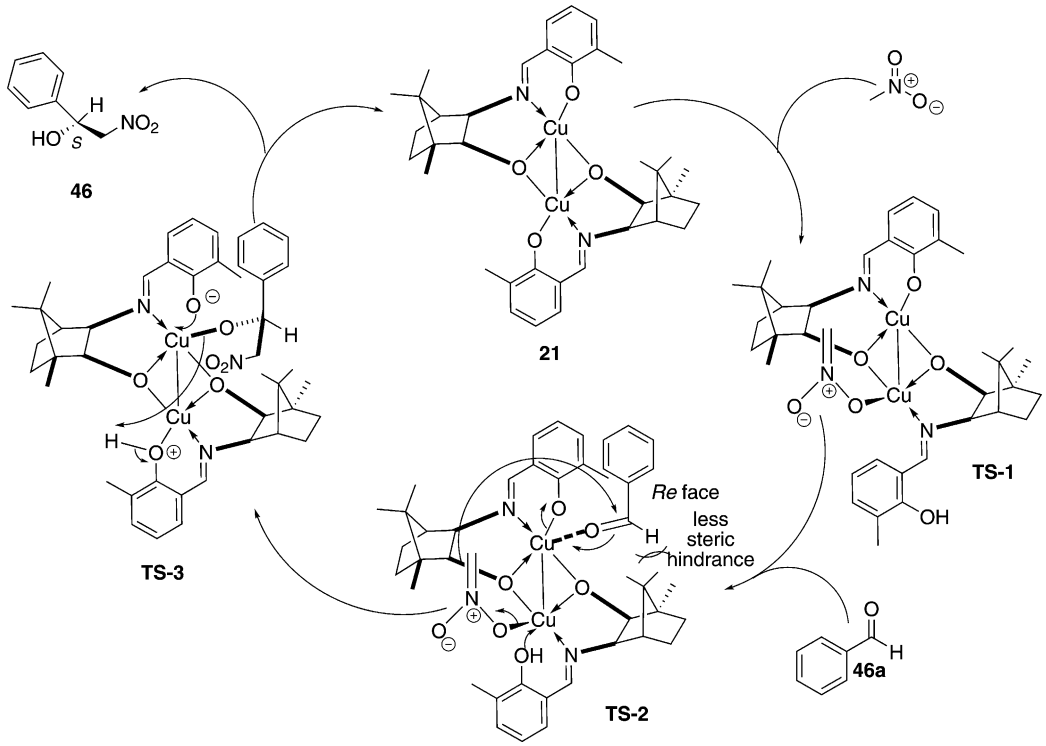
Entry	RCHO	R^1	Additive [mol%]	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]	
							syn	*anti*
1	**25a**	Me	none	120	28	56:44	43	63
2	**26a**	Me	none	120	51	59:41	76	77
3	**27a**	Me	none	120	62	66:34	96	96
4	**46a**	Me	none	120	35	55:45	68	69
5	**26a**	Me	4-$NO_2C_6H_4OH$ (10)	100	85	53:47	73	74
6	**25a**	Me	2,4-$Me_2C_6H_3OH$ (10)	96	76	52:48	55	67
7	**25a**	Me	2,4-(*t*-Bu)$_2C_6H_3OH$ (10)	96	74	57:43	61	78
8	**25a**	Me	3,4-$Cl_2C_6H_3OH$ (10)	96	81	57:43	80	90
9	**25a**	Me	4-$MeOC_6H_4OH$ (10)	96	92	58:42	80	93
10	**30a**	Me	4-$MeOC_6H_4OH$ (10)	120	60	55:45	89	80
11	**30a**	Me	4-$MeOC_6H_4OH$ (25)	120	99	55:45	94	84
12	**30a**	Me	4-$MeOC_6H_4OH$ (50)	120	99	54:46	94	91
13	**30a**	Me	4-$MeOC_6H_4OH$ (75)	120	99	52:48	94	90
14	**30a**	Me	4-$MeOC_6H_4OH$ (100)	120	99	57:43	93	89
15	**25a**	Me	4-$MeOC_6H_4OH$ (50)	120	86	56:44	84	86
16	**26a**	Me	4-$MeOC_6H_4OH$ (50)	120	88	60:40	80	80
17	**27a**	Me	4-$MeOC_6H_4OH$ (50)	120	90	63:37	90	94
18	**33a**	Me	4-$MeOC_6H_4OH$ (50)	120	82	58:42	98	76
19	**36a**	Me	4-$MeOC_6H_4OH$ (50)	120	51	57:43	91	86
20	**42a**	Me	4-$MeOC_6H_4OH$ (50)	120	72	57:43	95	91
21	**46a**	Me	4-$MeOC_6H_4OH$ (50)	120	99	55:45	77	74
22	**30a**	Me	$PhCO_2H$ (10)	120	98	57:43	94	96
23	**25a**	Me	$PhCO_2H$ (10)	100	88	55:45	87	98
24	**26a**	Me	$PhCO_2H$ (10)	100	90	59:41	85	86
25	**27a**	Me	$PhCO_2H$ (10)	100	94	64:36	97	97
26	**33a**	Me	$PhCO_2H$ (10)	100	80	56:44	98	81
27	**36a**	Me	$PhCO_2H$ (10)	100	98	57:43	92	87
28	**42a**	Me	$PhCO_2H$ (10)	100	81	58:42	65	83
29	**46a**	Me	$PhCO_2H$ (10)	96	82	59:41	84	83
30	**25a**	Et	4-MeC_6H_4OH (10)	120	40	61:39	81	82
31	**25a**	Et	$PhCO_2H$ (10)	120	58	60:40	85	82
32	**26a**	Et	$PhCO_2H$ (10)	120	63	59:41	85	93
33	**30a**	Et	$PhCO_2H$ (10)	120	53	55:45	89	91

[a] *Reaction conditions:* catalyst **21** (1 mol%, 0.01 equiv.) in *t*-BuOH/$R^1CH_2NO_2$ (20:20 vol) stirred for 1.5 h, additive addition, 1.5 h stirring and finally aldehyde (50 mg, 1 equiv.) addition and stirred for mentioned time.
[b] Yield refers to the chromatographically pure compounds.
[c] The *anti*/*syn* ratio was determined by ^{1}H NMR.
[d] The *ee*s of *syn* and *anti* forms were determined by chiral HPLC on various chiral columns.

hydes was then screened with 10 mol% $PhCO_2H$. All the aldehydes showed good yield and *ee* of diastereomeric mixtures (Table 4, entries 23–29). Even benzaldehyde (**46a**) yielded its product with a higher *ee* (Table 4, entry 29) compared to the result with 4-$MeOC_6H_4OH$. However, 2-bromobenzaldehyde (**42a**) showed an unreasonably moderate *ee*. This catalytic system was also investigated with regard to the scope of the Henry reaction with nitropropane. The products were furnished in moderate yields with good enantioselectivities (Table 4, entry 31–33) with 10 mol% $PhCO_2H$ as an additive. These results showed that this catalytic system is highly promising not only for nitromethane, but also for other nitroalkanes in the presence of achiral additive either 4-$MeOC_6H_4OH$ (50 mol%) or $PhCO_2H$ (10 mol%).

Proposed Mechanism for Chiral Induction

The observed absolute configuration of the Henry products obtained from the reaction of aldehydes



Scheme 2. Proposed mechanism for the absolute configuration of the Henry product (*S*)-**46** obtained from benzaldehyde **46a** and nitromethane.

with nitromethane is predicted by the proposed mechanism (Scheme 2). Benzaldehyde is taken as an example. Generally, a base or counter anion is needed to generate a nitronate anion in the Henry reaction. Hence the external base and the counter anion are absent in the present catalytic system; this must be a bifunctional catalytic system. The dimeric Cu complex (based on the X-ray) could be involved in the mechanism as proposed. Nitronate is considered to be formed by the removal of a proton by one of the phenoxides attached to the copper to give transition state-1 [**TS-1**]. Then the second copper could act as a Lewis acid which would coordinate with carbonyl oxygen of aldehyde to activate the electrophilicity of the carbonyl group as in **TS-2**. The aldehyde could arrange in such a fashion where steric hindrance between methyl groups in the camphor moiety and one of the two groups (H and Ph) in the aldehyde would become less as in **TS-2**. Furthermore, this **TS-2** arrangement would yield a π-π interaction between aldehyde phenyl group and phenyl group of Schiff base. The opposite arrangement would have stronger steric hindrance and almost no π-π interaction, therefore, **TS-2** would be the more favorable TS. The addition of nitronate to the *Re*-face of the aldehyde and cleavage from the catalyst through **TS-3** would then afford (*S*)-**46** and the regeneration of catalytic system.

Conclusions

In summary, this study shows that Cu_2(SBAIB-d)$_2$ **21** is an efficient catalyst for the asymmetric nitroaldol (Henry) reaction. Synthetically valuable Henry adducts were produced in excellent yields with high *ee* values for the reaction of various aldehydes with nitromethane. The merits of this catalytic system are its simplicity, mild reaction conditions, the need for as little as 1 mol% of catalyst **21**, an easy synthesis of catalyst in high yield, and the broad generality of the aldehyde including aromatic, polycyclic aromatic, heteroaromatic, α,β-unsaturated, branched, and unbrached aliphatic aldehydes. The present catalytic system also has a high substrate scope for nitroalkanes other than nitromethane. Although lower *de*s were obtained with nitroethane and nitropropane, excellent *ee* for both *syn* (up to 98%) and *anti* (up to 98%) diastereomers were obtained when either 50 mol% 4-$MeOC_6H_4OH$ or 10 mol% $PhCO_2H$ were added as an additive. Furthermore, this is the first Schiff base catalytic system that is highly effective for a wide range of substrates. Further studies of this catalyst for other asymmetric reactions will be reported in due course.

Experimental Section

General Procedure for Synthesis of Copper Complex of Aminoisoborneol Schiff Base $[Cu_2(SBAIB)]_2$

To a methanolic (40 vol) solution of aminoisoborneol Schiff base [(+)-SBAIB] (1 equiv.) in a single-neck round-bottom flask was added solid $Cu(OAc)_2{\cdot}H_2O$ (1.2 equiv.). The resulting yellowish green reaction mixture was stirred for 2 h at room temperature. Then solid NaOH (4 equiv.) was added to the above solution and stirring continued for 6 h. The resulting bluish solution was evaporated to dryness. To this residue was added brine and followed by extraction with benzene (4 times). The combined benzene layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to obtain the corresponding copper complex as a solid product, which was used for the asymmetric Henry reactions.

General Procedure for Catalytic Enantioselective Henry Reactions [Table 2]

A mixture of Cu_2[(+)-SBAIB-d]$_2$ **21** (1 mol%, 0.01 equiv.), *t*-BuOH (1 mL, 20 vol with respect to aldehyde) and $MeNO_2$ (1 mL, 20 vol with respect to aldehyde) in a screw-capped vial (8 mL) was stirred at room temperature for 3 h under atmospheric conditions. Then aldehyde (50 mg, 1 equiv.) was added to the above blue solution and stirred for the mentioned time. It was then quenched with 1 N HCl and the volatile material was evaporated by rotavapor to afford the crude product. This was purified by column chromatography (either 70–230 or 230–400 mesh silica gel). The resultant product was taken for the characterization. See the supporting informations for spectral data and HPLC spectra of Henry products.

General Procedure for Henry Reactions with Nitroethane and 1-Nitropropane [Table 4, entries 12–33]

A mixture of Cu_2[(+)-SBAIB-d]$_2$ (1 mol%, 0.01 equiv.), *t*-BuOH (1 mL, 20 vol) and either $EtNO_2$ or *n*-$PrNO_2$ (1 mL, 20 vol) in a vial (8 mL) was stirred at room temperature for 1.5 h. Then the additive either 4-$MeOC_6H_4OH$ (50 mol%, 0.5 equiv.) or $PhCO_2H$ (10 mol%, 0.1 equiv.) was added and the mixture stirred for another 1.5 h. Aldehyde (50 mg, 1 equiv.) was added and the resulting reaction mixture was stirred for the mentioned time. Afterwards, 1 N HCl was added to quench the reaction and the volatiles were evaporated by rotavapor to afford the crude product. This was then purified by column chromatography (either 70–230 or 230–400 mesh silica gel) and taken for the characterization.

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Copper Complex of Aminoisoborneol Schiff Base $Cu_2(SBAIB\text{-}d)_2$: An Efficient Catalyst for Direct Catalytic Asymmetric Nitroaldol (Henry) Reaction

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