Asymmetric Catalysis

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Three-Component Asymmetric Catalytic Ugi Reaction—Concinnity from Diversity by Substrate-Mediated Catalyst Assembly**

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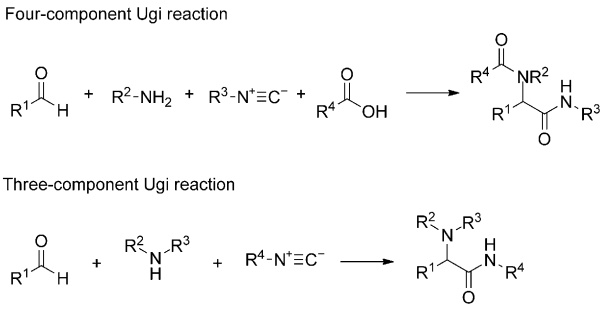
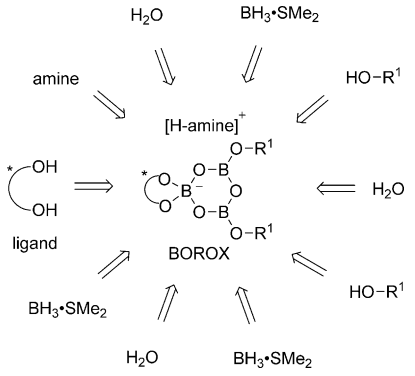
Abstract: *The first chiral catalyst for the three-component Ugi reaction was identified as a result of a screen of a large set of different BOROX catalysts. The BOROX catalysts were assembled in situ from a chiral biaryl ligand, an amine, water, $BH_3{\cdot}SMe_2$, and an alcohol or phenol. The catalyst screen included 13 different ligands, 12 amines, and 47 alcohols or phenols. The optimal catalyst system (LAP 8-5-47) provided α-amino amides from an aldehyde, a secondary amine, and an isonitrile with excellent asymmetric induction. The catalytically active species is proposed to be an ion pair that consists of the chiral boroxinate anion and an iminium cation.*

Multi-component coupling reactions that produce α-amino amides from isonitriles have been of interest ever since the first example of this process, which was discovered by Ugi in 1959.[1] Since that time, the Ugi reaction has been extensively studied and widely used in organic synthesis;[2,3] the diversity that is associated with the coupling of many components is one of its most salient attractions.[4] The four-component Ugi reaction can tolerate variations in the amine component (primary or secondary amines, hydrazines, and hydroxylamines) and in the acid component (carboxylic acids, hydrazoic acids, cyanates, thiocyanates, secondary amine salts, water, H_2S, H_2Se; Scheme 1).[2] The Ugi reaction can also be effected in the absence of the acid component in a three-component fashion; in this case, the amine component can be either a primary or a secondary amine.[5,6] The Ugi reaction can be catalyzed by both Brønsted and Lewis acids.[7] Pan and List were recently the first to report turnover for a three-component Ugi reaction with a primary amine and an achiral organocatalyst.[5] Unlike for the related Passerini reaction,[8] a chiral catalyst has yet to be reported for either the three- or the four-component Ugi reaction.[2d,4c,6,9] However, chiral catalysts have been reported for closely related Ugi-type processes that involve azomethine imines[10] or the formation of oxazoles from α-isocyanoacetamides.[11]

The Ugi reaction is commonly thought to involve an iminium ion,[2a,3,12] and the development of the first asymmetric catalytic Ugi reaction was an attractive target for an application of the BOROX catalysts that we have developed for asymmetric reactions that involve iminium ions in aziridinations,[13] aza-Cope rearrangements,[14] and hetero-Diels–Alder reactions.[15] The BOROX catalyst consists of an ion pair containing a chiral boroxinate anion, while the corresponding cation is derived from the protonated substrate.[16] The BOROX catalyst is typically assembled in situ from a ligand, $B(OPh)_3$, and an imine (or amine; Scheme 2, $R^1 = Ph$).[17] We have also shown that the same BOROX catalyst can be directly assembled in the presence of a molecule of an imine (or amine) from the ligand, three molecules of $BH_3{\cdot}SMe_2$, three molecules of water, and two molecules of phenol.[13d,e,18] This method should allow for the facile and diversity-oriented generation of an array of BOROX catalysts by incorporation of different ligands and different phenols or alcohols into the boroxinate core during in situ catalyst assembly (Scheme 2).[19] This essentially instant access to diversity has enabled the identification of the first effective chiral catalyst for the three-component Ugi reaction.



Scheme 1. Four- and three-component Ugi reactions.



Scheme 2. Catalyst diversity by in situ substrate-induced assembly.

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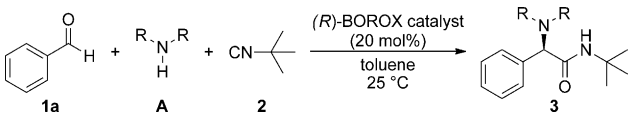
While optimizing the reaction conditions for the Ugi reaction of benzaldehyde and *tert*-butyl isonitrile with the BOROX catalyst that is derived from phenol (**P-11**) and the VAPOL ligand **L-4** (VAPOL = 2, 2′-diphenyl-[3, 3′-biphenanthrene]-4,4′-diol), it was found that the use of primary amine **A-6** only led to formation of imine **4** in quantitative yield (Table 1, entry 6). A number of secondary amines, including diethylamine, pyrrolidine, and aniline derivatives, did not produce a detectable amount of the desired product under these conditions. The reaction with pyrrolidine was examined more closely, and it was found that the only identifiable compound that was present in the reaction mixture aside from the starting materials was aminal **5** (50%; entry 1). Dibenzylamine **A-5** was found to give the Ugi product **3a** in 76% yield, but unfortunately only with an enantioselectivity of 59:41 e.r. (entry 5). The use of bis(*p*-methoxybenzyl)amine (**A-7**) gave essentially the same result (entry 7). The catalyst that is derived from the VANOL ligand **L-1** (VANOL = 3,3′-diphenyl-[2,2′-binaphthalene]-1,1′-diol) gave an even lower enantioselectivity. The most effective catalyst among those that are derived from the BINOL ligands **L-10** to **L-13** led to the formation of the Ugi product with 55:45 e.r., but with a reduced yield compared to the VAPOL catalyst (entries 9–12).

The next two phases of the screening process involved 1) the evaluation of 38 different BOROX catalysts that were all prepared from the VAPOL ligand and various alcohols/phenols, and 2) using the phenol/alcohol that is found to be most effective during this study in combination with newly prepared derivatives of the VANOL and VAPOL ligands. The results for a selected set of eight of the 38 phenol/alcohols that were used to generate VAPOL BOROX catalysts are given in Table 2 (see also the Supporting Information). The phenol/alcohol that leads to the most selective catalyst with VAPOL is 2,4,6-trimethylphenol (**P-36**); the desired product was obtained with an enantioselectivity of 70:30 e.r. (Table 2, entry 8). The electronic nature of the phenol does not have a significant effect on the asymmetric induction (entries 1 vs. 5). Essentially, the same induction was observed with tertiary and secondary alcohols as with phenol (**P-11**), but the use of ethanol stopped the reaction (not shown). The use of either (−)-menthol or (+)-menthol gave the product with the same sense of chirality, which indicates that chiral centers on the alcohol component may not be used for modifying the enantioselectivity. A series of BOROX catalysts that contain 2,4,6-trimethylphenol (**P-36**) were then generated from a series of newly prepared VANOL and VAPOL ligands. Catalysts that are prepared from **P-36** and the 7,7′-disubstituted VANOL derivatives **L-2** and **L-3** were hardly any more selective (entries 10 and 11) than those from the parent VANOL ligand, which essentially gave racemic material (entry 9).[20] However, the substituted VAPOL ligands **L-5** to **L-9** were generally significantly more selective than the parent VAPOL ligand. The optimal BOROX catalyst is obtained from the VAPOL derivative **L-8** and gave an e.r. of 85:15 (entry 15). The synergism between the ligand and the phenol components on the asymmetric induction was revealed experimentally: Whereas the enantioselectivity increased only slightly when the substituted VAPOL ligand **L-8** was used instead of VAPOL in combination with phenol (**P-11**; entries 17 vs. 4), a much higher enantioselectivity was observed when **L-8** was used instead of VAPOL with **P-36** (entries 15 vs. 8).

Table 1: Initial screen with amines and VANOL, VAPOL, and BINOL ligands.[a]



1a A 2 3

Entry	Ligand	Amine	Catalyst	*t* [h]	Yield[b] [%]	e.r.[c]
1	**L-4**	**A-1**	LAP 4-1-11	19	n.d.[d]	–
2	**L-4**	**A-2**	LAP 4-2-11	24	n.d.	–
3	**L-4**	**A-3**	LAP 4-3-11	24	n.d.	–
4	**L-4**	**A-4**	LAP 4-4-11	24	n.d.	–
5	**L-4**	**A-5**	LAP 4-5-11	24	76	41:59[e]
6	**L-4**	**A-6**	LAP 4-6-11	18	n.d.[f]	–
7	**L-4**	**A-7**	LAP 4-7-11	48	82	57:43
8	**L-1**	**A-5**	LAP 1-5-11	36	60	47:53[e]
9	**L-10**	**A-5**	LAP 10-5-11	40	9[g]	44:56[e]
10	**L-11**	**A-5**	LAP 11-5-11	24	37	55:45
11	**L-12**	**A-5**	LAP 12-5-11	43	30	55:45
12	**L-13**	**A-5**	LAP 13-5-11	24	trace	–

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.25 mmol, 0.2 M), amine (2.0 equiv), and **2** (1.5 equiv) in toluene at RT for the indicated time with 20 mol% of the catalyst. The pre-catalyst was prepared by heating a mixture of the *R*-configured ligand **L** (20 mol%), phenol (**P-11**; 40 mol%), H_2O (60 mol%), and $BH_3{\cdot}SMe_2$ (60 mol%) in toluene at 100 °C for 1 h. After removal of all volatile components, the BOROX catalyst was generated in situ by the addition of the amine at RT; this was followed by the addition of the aldehyde and then the isonitrile. [b] Yield of isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis. [d] Aminal **5** was formed in 50% yield (determined by ^{1}H NMR spectroscopy), amide **3** could not be detected. Heating this mixture at 80 °C for 18 h resulted in a complex mixture with **3** still not detectable. [e] Catalyst generated from the *S* ligand. [f] Imine **4** was formed quantitatively as determined by ^{1}H NMR spectroscopy with an internal standard. After 89 h, the imine was still present in quantitative amounts. [g] Yield determined by ^{1}H NMR spectroscopy with an internal standard. n.d. = not detected.

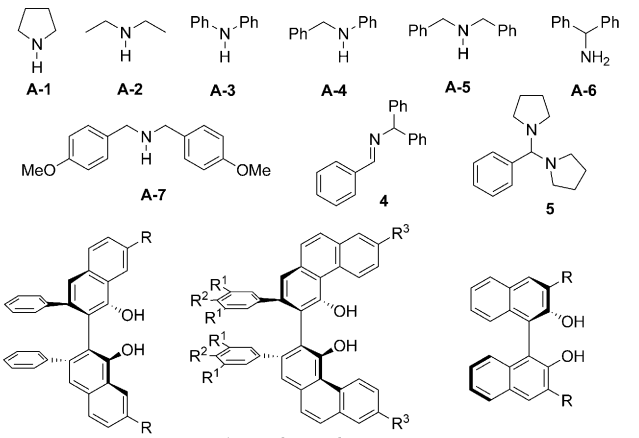
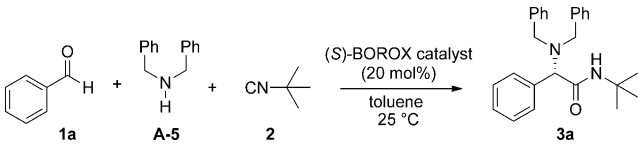


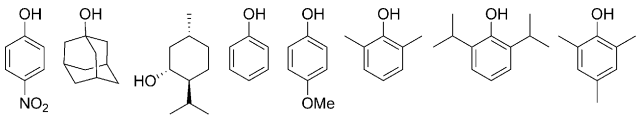
Table 2: Synergism by an appropriate choice of substituents at the boroxinate core.[a]



1a A-5 2 3a

Entry	Ligand	ROH	Catalyst	*t* [h]	Yield[b] [%]	e.r.[c]
1	**L-4**	**P-3**	LAP 4-5-3	36	64	57:43
2	**L-4**	**P-5**	LAP 4-5-5	39	86	58:42
3	**L-4**	**P-6**	LAP 4-5-6	24	91	58:42
4	**L-4**	**P-11**	**LAP 4-5-11**	**24**	**76**	**59:41**
5	**L-4**	**P-13**	LAP 4-5-13	36	75	59:41
6	**L-4**	**P-26**	LAP 4-5-26	39	82	64:36
7	**L-4**	**P-28**	LAP 4-5-28	39	71	60:40
8	**L-4**	**P-36**	**LAP 4-5-36**	**36**	**72**	**70:30**
9	**L-1**	**P-36**	LAP 1-5-36	39	52	49:51[d]
10	**L-2**	**P-36**	LAP 2-5-36	42	62	54:46
11	**L-3**	**P-36**	LAP 3-5-36	45	62	52:48
12	**L-5**	**P-36**	LAP 5-5-36	39	89	74:26
13	**L-6**	**P-36**	LAP 6-5-36	39	64	35:65[d]
14	**L-7**	**P-36**	LAP 7-5-36	39	93	74:26
15	**L-8**	**P-36**	**LAP 8-5-36**	**39**	**94**	**15:85[d]**
16	**L-9**	**P-36**	LAP 9-5-36	42	90	71:29
17	**L-8**	**P-11**	**LAP 8-5-11**	**39**	**74**	**62:38[e]**
18	**L-8**	**P-26**	LAP 8-5-26	39	93	78:22[e]

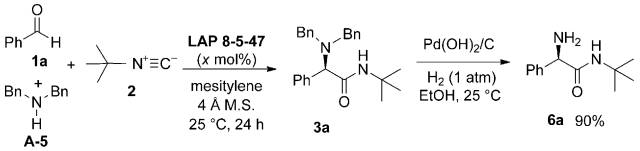
[a] Unless otherwise specified, all reactions were carried out with **1a** (0.25 mmol, 0.2 M), **A-5** (2.00 equiv), and **2** (1.5 equiv) in toluene at RT for the indicated time with 20 mol% of the catalyst. The catalyst was made from the *S* enantiomer of the ligand (≥99% *ee*) according to the procedure described in Table 1. [b] Yield of isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis. [d] Catalyst generated from the *R* ligand. [e] Ligand with 97% *ee*.



P-3 P-5 P-6 P-11 P-13 P-26 P-28 P-36

At this point, a solvent screen was performed with the optimized catalyst system, which is prepared from the substituted VAPOL ligand **L-8** and 2,4,6-trimethylphenol (**P-36**; see the Supporting Information). The asymmetric induction dropped substantially with coordinating solvents such as THF and acetonitrile (54:46 and 64:36 e.r., respectively), which is consistent with an ion pair mechanism. Mesitylene was found to be the most suitable solvent (87:13 e.r.; Table 3, entry 6), and all further optimization reactions were performed in this solvent. The stoichiometry of the amine with respect to the other components does not seem to have a strong impact on the reaction as the yields and enantioselectivities decreased only slightly in the range of 2.0 to 1.02 equivalents (entries 6–8). With the identification of the VAPOL derivative **L-8** as the optimal ligand, a final screen of this ligand and 13 different phenols was performed in mesitylene (for selected results, see Table 3; see also the Supporting Information). 2,6-Dimethyl-4-methoxyphenol (**P-47**) was found to be the most suitable phenol, and the resultant catalyst (LAP 8-5-47) gave the desired product with an enantiomeric ratio of 90:10 in 91% yield (entry 13). In contrast to the VAPOL-derived catalysts, which are insensitive to the electronic nature of the phenol (Table 2, entries 1 vs. 5), the catalysts that are derived from the VAPOL derivative **L-8** are quite sensitive to the nature of the phenol. The asymmetric induction slightly increased when the *p*-methyl group in **P-36** was replaced by a methoxy group (**P-47**; entries 6 vs. 13) and decreased significantly when a nitro-substituted phenol was employed (**P-44**; entries 6 vs. 12). This is consistent with an ion pair mechanism in which the strength of the electrostatic attraction is important for the asymmetric induction (Scheme 4). The procedure that was optimized for amine **A-5** (entry 13) was applied to several *para*-substituted dibenzylamines. All of these dibenzylamines gave high selectivities (87:13–90:10 e.r.; entries 13–17) with the exception of the *para*-nitro-substituted dibenzylamine **A-11**, which led to a substantial decrease in yield and enantioselectivity (entry 18); this result could be due to the destabilization of iminium ion **7** (Scheme 4).

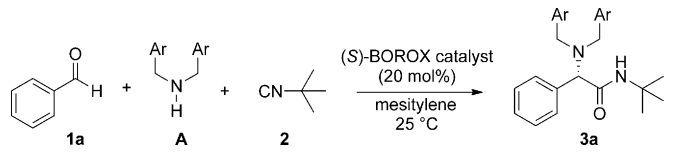
Having established the most effective combination of all of the parts of the boroxinate catalyst, different aryl aldehydes were evaluated as substrates for the Ugi reaction with amine **A-5** (Table 4). Most of the substrates, including aryl aldehydes with both electron-withdrawing and electron-donating groups, reacted to give α-amino amides with enantiomeric ratios of 90:10 to 95:5. The reaction of cyclohexane carboxaldehyde gave racemic product (47% yield, not shown); this result will require further examination. The reactions that are shown in in Table 4 were performed in the presence of 4 Å molecular sieves (M.S.), whereas most of the previous reactions in this work had been run in the absence of molecular sieves. The sieves have essentially no effect on the enantioselectivity, but seem to accelerate the reaction slightly. The rate is slower at 0 °C than at 25 °C, but the asymmetric inductions are not substantially different. In many cases, the α-amino amide **3** can be recrystallized, and a few examples are shown for which the e.r. could be enhanced to > 99.5:0.5. The ligand **L-8** can also be recovered from these reactions in high yield (ca. 90%) with no loss in enantiomeric purity (> 99.5:0.5 e.r.). The reaction can be extended to heterocyclic aldehydes, as illustrated by the reaction with pyridine carboxaldehydes. 3-Pyridyl carboxaldehyde is the most reactive coupling partner, whereas the 4-pyridyl isomer reacted more slowly (entries 27 and 28), and the 2-pyridyl isomer did not react at all (not shown).



	time (h)	sieves	yield (%) **3a**	e.r. **3a**	yield **3a** (%) first crop	e.r. **3a** first crop
20 mol% catalyst	23	yes	86	90 : 10	71	>99.5 : 0.5
10 mol% catalyst	30	yes	83	87 : 13	70	>99.5 : 0.5
20 mol% catalyst	38	no	88	90 : 10		
10 mol% catalyst	50	no	68	71 : 29		

Scheme 3. Effect of molecular sieves on yield and enantioselectivity at different catalyst loadings. Bn = benzyl.

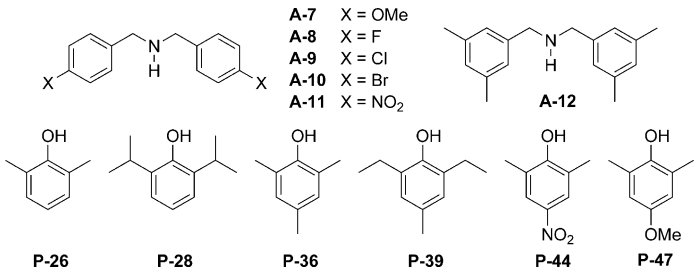
Table 3: Screen of additional phenols and amines with ligand **L-8**.[a]



1a **A** **2** **3a**

Entry	Ligand	Amine	ROH	Catalyst	*t* [h]	Yield[b] [%]	e.r.[c]
1	**L-4**	**A-5**	**P-11**	LAP 4-5-11	38	71	61:39
2	**L-4**	**A-5**	**P-36**	LAP 4-5-36	42	90	71:29
3	**L-8**	**A-5**	**P-11**	LAP 8-5-11	41	72	33:67[d]
4	**L-8**	**A-5**	**P-26**	LAP 8-5-26	39	94	83:17
5	**L-8**	**A-5**	**P-28**	LAP 8-5-28	39	72	68:32
6	**L-8**	**A-5**	**P-36**	LAP 8-5-36	39	92	87:13
7	**L-8**	**A-5**	**P-36**	LAP 8-5-36	39	86	86:14[e]
8	**L-8**	**A-5**	**P-36**	LAP 8-5-36	39	75	84:16[f]
9	**L-8**	**A-12**	**P-36**	LAP 8-12-36	39	65	61:39
10	**L-6**	**A-5**	**P-36**	LAP 6-5-36	41	53	32:68[d]
11	**L-8**	**A-5**	**P-39**	LAP 8-5-39	38	95	82:18
12	**L-8**	**A-5**	**P-44**	LAP 8-5-44	38	76	59:41
13	**L-8**	**A-5**	**P-47**	LAP 8-5-47	38	91	10:90[d,g,h]
14	**L-8**	**A-7**	**P-47**	LAP 8-7-47	24	91	12:88[d]
15	**L-8**	**A-8**	**P-47**	LAP 8-8-47	24	85	10:90[d]
16	**L-8**	**A-9**	**P-47**	LAP 8-9-47	24	80	12:88[d]
17	**L-8**	**A-10**	**P-47**	LAP 8-10-47	24	79	13:87[d]
18	**L-8**	**A-11**	**P-47**	LAP 8-11-47	24	22	27:73[d]

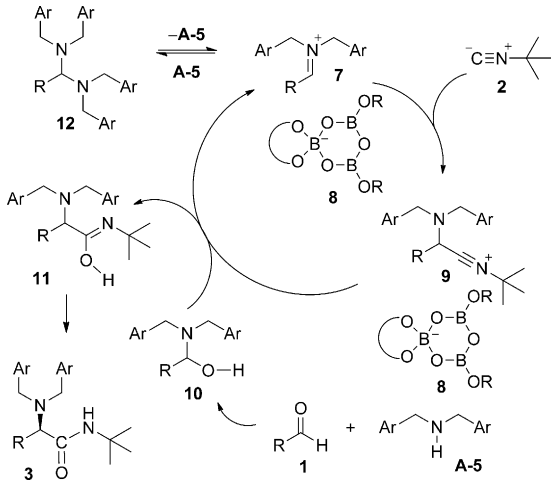
[a] Unless otherwise specified, all reactions were carried out with **1a** (0.25 mmol, 0.2 M), amine (2.0 equiv), and **2** (1.5 equiv) in mesitylene at RT for the indicated time with 20 mol% of the catalyst. Entries 14–18 were carried out in the presence of 4 Å molecular sieves. The catalyst was prepared according to the procedure in Table 1 with the *S* ligand unless otherwise specified. (*S*)-**L-8**: 97% *ee*; (*R*)-**L-8**, (*S*)-**L-4**, and (*R*)-**L-6:** >99% *ee*. [b] Yield of isolated product after column chromatography on silica gel. [c] Determined by HPLC analysis. [d] Catalyst generated from the *R* ligand. [e] Amine (1.2 equiv). [f] Amine (1.02 equiv). [g] 89:11 e.r. with (*S*)-**L-8** (97% *ee*). [h] 86% yield after 24 h.



Although *tert*-butyl isonitrile was the optimal isonitrile, a number of other isonitriles were suitable substrates for the reaction with benzaldehyde and gave the corresponding products with enantioselectivities ranging from 51:49 to 88:12 e.r. under the conditions that are described in Table 4 (see the Supporting Information). The catalyst loading can be reduced to 10 mol% with no significant drop in yield or asymmetric induction when molecular sieves are employed (Scheme 3). The e.r. drops from 90:10 to 87:13 when the catalyst loading is reduced from 20 mol% to 10 mol%.[21] Both of these the mixtures (90:10 and 87:13 e.r.) were recrystallized to give the product with an enhanced e.r. of >99.5:0.5 in 70–71% recovery yield for the first crop. The absolute configuration was determined by removal of the benzyl groups to give **6a**; the other α-amino amides were assumed to be homochiral with **3a**.

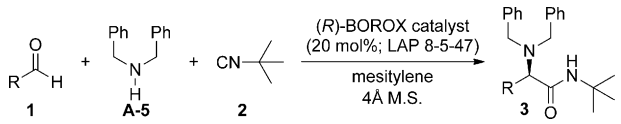
The involvement of a BOROX catalyst that contains a boroxinate core is supported by ^{1}H and ^{11}B NMR studies (see the Supporting Information). It is considered to be likely that the boroxinate anion **8**, which exists as an ion pair with the iminium ion **7**, acts as the catalyst; therefore, this Ugi reaction is an example of "chiral anion catalysis".[22] The mechanism can be envisioned to involve the addition of the isonitrile to the iminium cation **7** to give the nitrilium cation **9**, which also exists as an ion pair with the chiral anion catalyst **8** (Scheme 4). We propose that the next step is exchange of the OH group between the nitrilium cation **9** and hemiaminal **10**, which would result in the regeneration of the iminium ion **7** and the formation of the product in the form of tautomer **11**. It is also possible that the hemiaminal **10** is protonated and releases H_2O, which adds to nitrilium ion **9**. Evidence against the presence of free H_2O in this reaction stems from the fact that the presence of molecular sieves does not greatly affect the rate of the reaction. Furthermore, the addition of H_2O slows down the reaction (see the Supporting Information, sections VIII and XVIII). When the reaction is followed by ^{1}H NMR spectroscopy, an initial build-up of aminal **12** (ca. 15% at ca. 25% conversion) was observed; the aminal then slowly disappears and is gone at the end of the reaction. Finally, a four-component version of this reaction with the optimized BOROX catalyst (LAP 8-5-47) was attempted with benzaldehyde and benzoic acid, but the product of this Ugi reaction was obtained as a racemic mixture (see the Supporting Information).

A great diversity of BOROX catalysts can be quickly generated, and the most suitable combination of the ligand, amine, and phenol/alcohol components of the catalyst was sought and found for the three-component asymmetric Ugi reaction. The catalytically active species is proposed to involve



Scheme 4. Proposed mechanism for the three-component Ugi reaction.

Table 4: Substrate scope of the catalytic asymmetric three-component Ugi reaction.[a]



1 A-5 2 3

Entry	Series	R	*t* [h]	T [°C]	Yield [%][b]	e.r.[c]
1	a	C_6H_5	7	40	87[e]	86:14
2[d]	a	C_6H_5	24	25	86 (71)	90:10 (>99.5:0.5)
3	a	C_6H_5	66	0	75	92:8
4[f]	b	4-$NO_2C_6H_4$	24	25	83	93:7
5[f]	b	4-$NO_2C_6H_4$	66	0	51[e]	92:8
6	c	4-$CF_3C_6H_4$	24	25	85	91:9
7	d	4-BrC_6H_4	24	25	85	93:7
8	d	4-BrC_6H_4	48	0	65[g]	95:5
9[f]	d	4-BrC_6H_4	48	0	75[h,i]	95:5
10[f]	e	3-BrC_6H_4	22	25	82	93:7
11	e	3-BrC_6H_4	66	0	66[h]	92:8
12	f	3,4-$Cl_2C_6H_3$	24	25	85	94:6
13	f	3,4-$Cl_2C_6H_3$	66	0	54[e]	95:5
14	g	4-FC_6H_4	24	25	87[e]	91:9
15	g	4-FC_6H_4	67	0	62	94:6
16	h	4-$MeO_2CC_6H_4$	24	25	80	93:7
17[f]	h	4-$MeO_2CC_6H_4$	67	0	62	93:7
18	i	4-$AcOC_6H_4$	24	25	86	85:15
19	j	4-$AcNHC_6H_4$	24	25	77 (47)	85:15 (96:4)
20[f]	k	4-MeC_6H_4	24	25	84 (47)	91:9 (>99.5:0.5)
21	k	4-MeC_6H_4	66	0	80[e]	92:8
22	l	2-MeC_6H_4	24	25	76 (56)	78:22 (>99:1)
23	m	4-*t*BuC_6H_4	24	25	83	84:16
24	n	4-$MeOC_6H_4$	40	25	84[j]	88:12
25	n	4-$MeOC_6H_4$	24	25	70	89:11
26	n	4-$MeOC_6H_4$	66	0	51	92:8
27	o	3-pyridyl	25	25	80 (61)	90:10 (>99:1)
28	p	4-pyridyl	70	25	66	89:11

[a] Unless otherwise specified, all reactions were carried out with **1** (0.25 mmol, 0.2 M), amine (2.0 equiv), and **2** (1.5 equiv) in mesitylene at RT in the presence of 4 Å M.S. for the indicated time with 20 mol% of the catalyst. The catalyst was made from the *R* enantiomer of the ligand (≥99% *ee*) according to the procedure in Table 1. [b] Yield of isolated product after chromatography on silica gel. The value in parentheses denotes the recovery yield for the first crop of the recrystallization. [c] Determined by HPLC analysis. The e.r. values in parentheses are for the first crop. [d] Average of four runs. [e] Yield determined by ^{1}H NMR spectroscopy with an internal standard (Ph_3CH). [f] Average of two runs. [g] 46% yield after 24 h. [h] Reaction at 0.4 M. [i] 76% yield after 66 h. 60% yield after 66 h in the absence of 4 Å M.S. [j] No 4 Å M.S.

an ion pair between a chiral boroxinate anion and an achiral iminium ion.

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