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The Direct Asymmetric Alkylation of α-Amino Aldehydes with 3-Indolylmethanols by Enamine Catalysis

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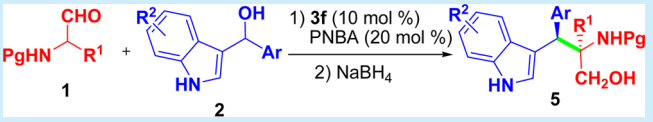
Supporting Information

ABSTRACT: This work describes an efficient α-alkylation reaction of α-amino aldehydes with 3-indolylmethanols. In the promotion of catalyst **3f**, the target products were obtained in high yields (up to 99%), good diastereoselectivities (up to 88:12), and excellent enantioselectivities (up to 96% ee). The direct alkylation products can be readily converted into other tryptophan derivatives without the loss of stereoselectivities.



The catalytic asymmetric alkylation of carbonyl compounds is an important C−C bond-forming strategy in organic synthesis,[1] and a diverse range of organocatalytic asymmetric alkylation reactions have been developed during the course of the past two decades for the construction of optically active molecules.[2] In 2009, Cozzi et al.[3] reported the first asymmetric alkylation of aldehydes, which used active biarylmethanols as the alkylating agents by enamine catalysis. In the same year, we reported the results of our pioneering study toward the development of an alkylation reaction of emanides with 3-indolylmethanols by Brønsted acid catalysis.[4] Alcohols are ideal reagents for the alkylation of carbonyl compounds because water is produced as the only byproducts, making the development of novel alkylation reactions between various nucleophiles and active alcohols increasingly attractive from a green chemistry perspective.[2] Numerous carbonyl compounds have been employed in asymmetric alkylation reactions of this type, including aldehydes,[5] ketones,[6] and carbonyl derivatives,[7] where they were alkylated with biarylmethanols. α-Amino aldehydes, which are an important class of carbonyl compounds, can be readily prepared from natural and unnatural α-amino acids and α-amino nitriles,[8] and these compounds can be used as starting materials for the synthesis of novel optically active α-amino aldehydes, α-amino acid, and amino alcohol precursors. However, building blocks of this type are seldom used in organocatalytic asymmetric synthesis and, to the best of our knowledge, there have only been three examples reported in the literature to date. The first of these reports involves the L-proline catalyzed aldol addition of α-amino aldehydes to aliphatic aldehydes,[9] whereas the second involves the chiral primary amine catalyzed Michael addition of α-amino aldehydes to vinyl sulfones.[8] Most recently, Maruoka et al. reported an aldol reaction between α-amino acetaldehyde and a series of different aldehydes.[10] Given the limited number of publications in this area, there is still plenty of scope for the development of novel methodology involving the use of α-amino aldehydes in organocatalytic asymmetric reactions. In continuation of our work toward the development of new strategies for the alkylation of carbonyl compounds with biarylmethanols,[4,11] we report herein the first direct asymmetric alkylation reaction of α-amino aldehydes with 3-indolylmethanols by enamine catalysis. This method allowed for the synthesis of a structurally diverse range of α,β-disubstituted tryptophan[12] precursors in good yields and excellent enantioselectivities.

This particular study started as an investigation of the L-proline-catalyzed reaction[13] between N-Boc protected α-amino aldehyde **1a** and 3-indolylmethanol **2a**. Unfortunately, however, the desired reaction did not take place in this case. The results of our previous work indicated that chiral primary-amine-thioureas are suitable organocatalysts for the direct α-alkylation of aldehydes with 3-indolylmethanols. With this in mind, catalyst **3a** was added to the reaction of **1a** and **2a** and the target product **4a** was obtained in 82% yield with moderate enantioselectivity (Table 1, entry 2). Based on the success of this reaction, we proceeded to investigate the effectiveness of catalysts **3b**−**e**. Pleasingly, all four of these catalysts performed well in this reaction to give the desired product **4a** with a good chiral induction, although the diastereoselectivities were very poor (Table 1, entries 3−6). The use of catalyst **3f** in the reaction led to an increase in the enantioselectivity of the major diastereoisomer of **4a** to 92% ee, as well as a significant increase in the diastereoselectivity (Table 1, entry 7). Catalyst **3g**, which was prepared from (1*S*,2*R*)-2-amino-1,2-diphenylethanol, was then used to investigate the compatibility of these two chiral units. Unfortunately, however, the use of this catalyst led to a slight reduction in enantio- and diastereoselectivity of the reaction, as well as a significant decrease in the yield of **4a** (Table 1, entry 8). Catalysts **3h** and **3i**, which were derived from (1*S*,2*S*)-cyclohexane-1,2-diamine and 1,2-diphenylethane-1,2-diamine, respectively, were also tested in this reaction, but neither of these catalysts performed as well as **3f** (Table 1, entries 9 and 10). Catalysts **3j**−**m** were also prepared and evaluated in terms of their ability to promote the reaction between **1a** and **2a**. Unfortunately, although catalysts **3j**−**l** promoted this reaction, they gave poor yields of the desired

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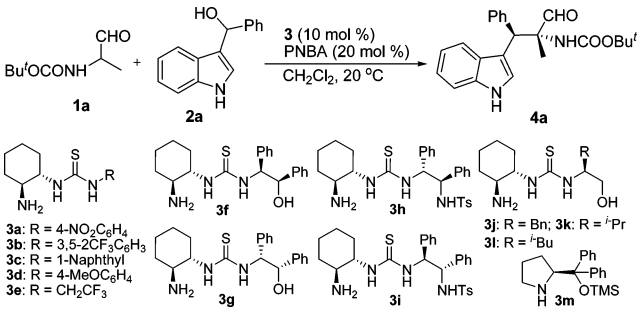
Table 1. Screening of the Catalysts



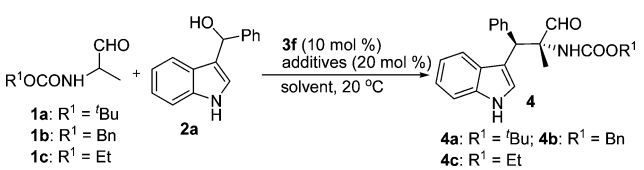
entry	3	t (h)	y (%)[a]	dr[b]	ee[c]
1	L-proline	48	–	–	–
2	**3a**	46	82	46:54	41/80
3	**3b**	46	89	45:55	52/81
4	**3c**	52	80	50:50	55/70
5	**3d**	55	51	45:55	48/80
6	**3e**	46	91	48:52	68/76
7	**3f**	48	93	24:76	73/92
8	**3g**	51	60	32:68	78/88
9	**3h**	51	75	29:71	40/70
10	**3i**	51	82	34:66	77/84
11	**3j**	69	50	43:57	53/50
12	**3k**	69	56	43:57	43/59
13	**3l**	69	55	44:56	51/60
14	**3m**	48	trace	ND[d]	ND

[a]Isolated yield of the two diastereoisomers. [b]Determined by HPLC. [c]Determined by chiral HPLC. [d]ND = Not Determined.

product with low levels of enantio- and diastereoselectivity (Table 1, entries 11–13). Notably, catalyst **3m**, which has been used extensively in organocatalysis,[14] failed to promote this reaction (Table 1, entry 14). Based on these results, catalyst **3f** was selected as the optimal catalyst to further optimize the reaction conditions.

With the optimal catalyst in hand, we proceeded to screen some of the other reaction conditions (Table 2). The nature of

Table 2. Optimization of the Reaction Conditions



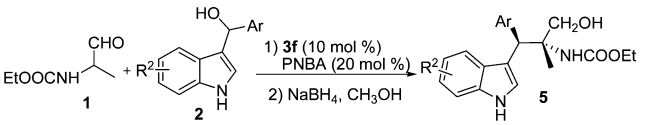
entry	additives	solvent	y (%)[a]	dr[b]	ee (%)[c]
1	BA	CH_2Cl_2	43	49:51	40/52
2	PNBA	CH_2Cl_2	93	24:76	73/92
3	DNBA	CH_2Cl_2	86	28:72	66/85
4	*o*-FBA	CH_2Cl_2	64	40:60	80/72
5	PNBA	$CHCl_3$	87	26:74	94/91
6	PNBA	$PhCH_3$	33	21:79	84/92
7	PNBA	THF	trace	ND[d]	ND
8	PNBA	CH_2Cl_2	80	22:78	–/94[e]
9	PNBA	CH_2Cl_2	48	21:79	–/94[f]
10	PNBA	CH_2Cl_2	87	32:68	69/87[g]
11	PNBA	CH_2Cl_2	99	24:76	72/-93[h]

[a]Isolated yield of the two diastereoisomers. [b]Determined by HPLC. [c]Determined by chiral HPLC. [d]ND = Not Determined. [e]At 10 °C. [f]At 0 °C. [g]Using **1b** as donor. [h]Using **1c** as donor.

the acid additive was found to have a significant impact on the outcome of the reaction (Table 2, entries 1–4), with *p*-nitrobenzoic acid (**PNBA**) providing the best results of all of the additives tested in the current study. The effect of the solvent was also investigated and found to have a significant impact on the yield and stereoselectivity of the reaction, and dichloromethane (DCM) was identified as the best solvent for this reaction (Table 2, entry 2). The effect of temperature was also investigated, and it was found that the enantioselectivity of the reaction increased slightly when the reaction was conducted at low temperature, but this also led to a decrease in the yield (Table 2, entries 8–9). The nature of the N-protecting group used in **1** also had a significant impact on the outcome of this reaction. For example, the reaction proceeded at a much greater rate when α-amino aldehyde **1c** was used as a donor, with compound **4c** being produced in excellent yield, with good diastereoselectivity and excellent enantioselectivity over a short reaction time (Table 2, entry 11).

With the optimal reaction conditions in hand, we proceeded to explore the substrate scope for this reaction using a variety of different 3-indolylmethanols (Table 3). The alkylation products

Table 3. Substrate Scope of 3-Indolylmethanols



entry	Ar, R^2	5	t (h)	y (%)[a]	dr[b]	ee (%)[c]
1	C_6H_5, H	**4c**	22	99	76:24	93
2	4-ClC_6H_4, H	**5a**	64	75	86:14	91
3	4-FC_6H_4, H	**5b**	64	70	88:12	96
4	4-BrC_6H_4, H	**5c**	70	75	88:12	90
5	4-$CF_3C_6H_4$, H	**5d**	132	63	77:23	93
6	3-ClC_6H_4, H	**5e**	110	76	81:19	87
7	2-BrC_6H_4, H	**5f**	117	76	82:18	94
8	4-$MeOC_6H_4$, H	**5g**	15	86	79:21	81
9	4-MeC_6H_4, H	**5h**	15	82	77:23	89
10	4-^{t}BuC_6H_4, H	**5i**	31	88	74:26	86
11	3-MeC_6H_4, H	**5j**	39	81	77:23	87
12	3-$MeOC_6H_4$, H	**5k**	28	94	70:30	86
13	2-$MeOC_6H_4$, H	**5l**	11	81	70:30	85
14	2-Naphthyl, H	**5m**	36	83	80:20	84
15	C_6H_5, 6-F	**5n**	88	80	79:21	89
16	C_6H_5, 5-Cl	**5o**	88	83	78:22	93
17	C_6H_5, 5-Br	**5p**	88	82	76:24	90
18	4-FC_6H_4, 5-Me	**5q**	22	84	83:17	94
19	4-FC_6H_4, 5-MeO	**5r**	27	87	71:29	91
20	4-FC_6H_4, 6-Me	**5s**	24	84	76:24	89
21	4-FC_6H_4, 7-Me	**5t**	34	82	79:21	90
22	4-BrC_6H_4, 6-Me	**5u**	96	87	85:15	90
23	2-BrC_6H_4, 7-Me	**5v**	117	72	74:26	92
24	2-ClC_6H_4, 7-Me	**5w**	96	71	76:24	92

[a]Isolated yield of the two diastereoisomers. [b]Determined by ^{1}H NMR; [c]ee of the major diastereomers determined by chiral HPLC.

were converted to the corresponding amino alcohols using $NaBH_4$ and then submitted to NMR and chiral HPLC analysis. A variety of different groups were introduced to the phenyl ring of the 3-indolylmethanol substrate **2**. The introduction of electron-withdrawing groups led to a slight reduction in the rate of the reaction, and extended reaction times were required to obtain the corresponding products **5a–f** in good yields (Table

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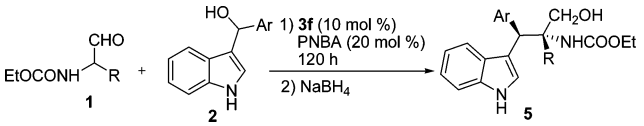
3, entries 2–7). Notably, however, 3-indolylmethanol substrates bearing electron-withdrawing groups tended to afford enhanced stereochemical outcomes. For example, the 3-inolymethanol substrate bearing a 4-F-phenyl substituent gave the corresponding alkylated product **5b** in 88:12 dr and 96% ee (Table 3, entry 3). In contrast, 3-indolylmethanols bearing an electron-rich substituted phenyl group gave the corresponding alkylation products in good yields and enantioselectivities, but with only moderate diastereoselectivities (Table 3, entries 8–13). The introduction of electron-rich phenyl substituents led to a dramatic increase in the rate of the reaction, which was attributed in part to their ability to rapidly form alkylideneindolenium intermediates during the course of the reaction compared to that of the electron-deficient phenyl substituted 3-indolylmethanols. The effects of placing different substituents on the indole ring of the 3-indolylmethanol substrate were also investigated. The results of these reactions revealed that electron-donating and -withdrawing substituents were well tolerated at the 5-, 6-, and 7-positions of the indole ring, with the corresponding products **5o–w** being formed in good yields and diastereoselectivities with excellent enantioselectivities (Table 3, entries 15–24).

This transformation was found to be particularly sensitive to the nature of the substituents on the α-amino aldehyde. For example, the use of bulky α-amino aldehydes such as ethyl (1-oxobutan-2-yl) carbamate led to a significant decrease in the yield and stereoselectivity, with the corresponding product **5x** being isolated in 60% yield and moderate stereoselectivities (Table 4, entry 1). Further increasing the size of the α-

Table 4. Substrate Scope of the α-Amino Aldehydes



entry	R, Ar	5	y (%)[a]	dr[b]	ee (%)[c]
1	Et, 4-BrC_6H_4	**5x**	60	75:25	79
2	^{n}Pr, 4-ClC_6H_4	**5y**	52	67:33	67
3	Bn, 4-BrC_6H_4	**5z**	41	34:66	−55

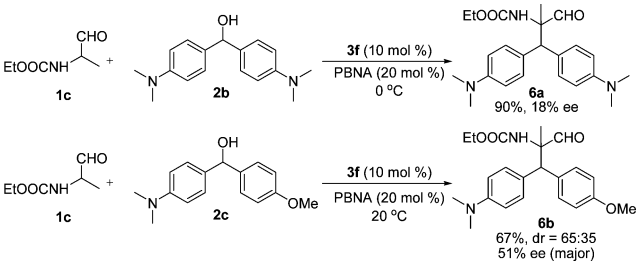
[a]Isolated yield of the two diastereoisomers. [b]Determined by ^{1}H NMR. [c]ee of the major diastereomers determined by chiral HPLC.

substituent led to further decreases in the yield and stereoselectivity of the reaction, as exemplified by the n-propyl and benzyl substituted α-amino aldehydes, which gave the corresponding products **5y** and **5z** in 52% and 41% yields, respectively, with poor enantio- and diastereoselectivities (Table 4, entries 2 and 3). These results therefore suggest that steric hindrance from the α-substituent was leading to the observed decrease in the yield and stereoselectivity of these reactions.

Biphenylmethanols have been used extensively as substrates in alkylation reactions involving carbonyl compounds.[5] With this in mind, we also evaluated the use of biphenylmethanols in the current reaction (Scheme 1). Although the alkylation products **6a** and **6b** were obtained in high yields under the optimized conditions, the enantio- and diastereoselectivities were very poor.

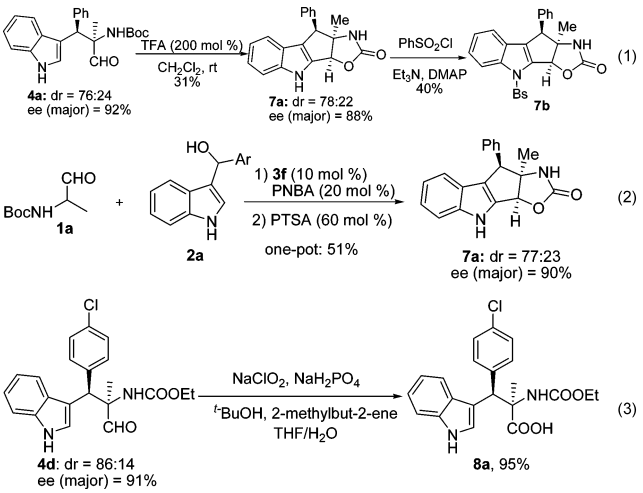
The alkylated indole products described above could be readily converted into a variety of novel indole compounds. For example, aldehyde **4a** was converted to cyclopenta[b]indole **7a**

Scheme 1. Alkylation of α-Amino Aldehyde 1c with Biphenylmethanols



in the presence of trifluoroacetic acid with a slight decrease in the enantioselectivity (Scheme 2, eq 1), albeit in a low yield of

Scheme 2. Synthesis of Novel Indoles from Compounds 4a and 4d



31%. After successfully optimizing the reaction conditions, we established that successive alkylation/cyclization reactions could be conducted in a one-pot manner to give the polycyclic product **7a** in good yield and excellent enantioselectivity (Scheme 2, eq 2). The alkylated indole products could also be used to prepare α,β-disubstituted tryptophan derivatives. For example, the oxidation of **4d** with $NaClO_2$ gave **8a** in excellent yield (Scheme 2, eq 3).[15] The relative and absolute configuration of **7b** was determined by single crystal X-ray analysis,[16] and the stereochemistries of compounds **4**, **5**, and **8a** were assigned accordingly.

In conclusion, we have developed an efficient reaction for the alkylation of α-amino aldehydes with 3-indolylmethanols. The alkylated products were obtained in high yields, with good diastereoselectivities and good to excellent enantioselectivities. Furthermore, the products resulting from this reaction could be converted into other indole derivatives without any discernible impact on their stereoselectivities.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterizations, and ^{1}H NMR, ^{13}C NMR, and HPLC spectra copies for all products as well as X-ray crystallographic data for compound **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1030822 (**7b**) 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.