Asymmetric Catalysis

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Catalytic Asymmetric Three-Component Synthesis of Homoallylic Amines**

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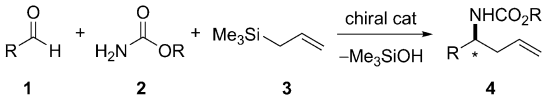
The direct catalytic three-component coupling of aldehydes (**1**), carbamates (or amines; **2**), and nontoxic allyltrimethylsilane (**3**) is a very effective approach to homoallylic amine derivatives **4** [Eq. (1)]. However, despite its great potential for the practical synthesis of chiral nitrogenous substances



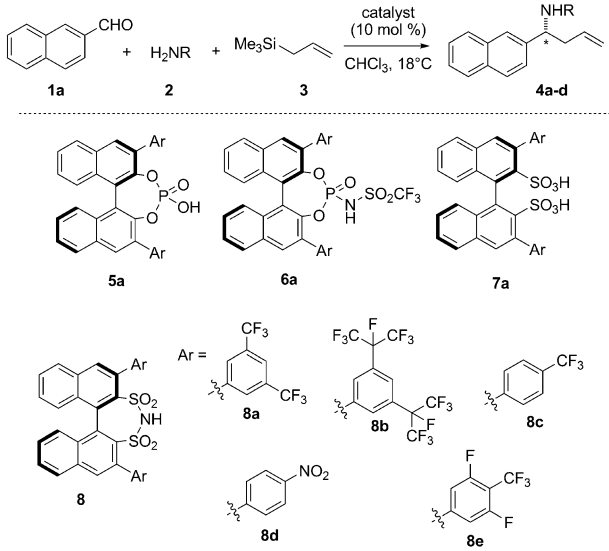
(1)

and the enormous progress of asymmetric catalysis over the last few decades, an enantioselective version of this reaction has been entirely unknown.[1–3] Herein we report our finding that the reaction of 9-fluorenylmethyl carbamate (Fmoc-NH_2) with a variety of aldehydes (**1**) and silane **3** in the presence of a new chiral disulfonimide catalyst furnishes the corresponding products **4** highly enantioselectively and in good yield.

We have recently introduced chiral enantiomerically pure disulfonimides (DSI) as highly active and enantioselective catalysts for the reaction of silylated nucleophiles with aldehydes.[4] Preliminary mechanistic studies suggest that these reactions proceed through an asymmetric counteranion-directed Lewis acid catalysis mechanism operated by an in situ silylated chiral disulfonimide.[5] While the ability of our DSI catalysts to activate other electrophiles such as imines has not yet been explored, we speculated on their potential applicability in the above three-component reaction. Although mechanistic details are currently unknown, we were tempted to hypothesize that this and related processes involve a silyl-transfer mechanism, and implies amenability to our silyl asymmetric counteranion-directed catalysis (ACDC) activation strategy. Our approach has proven particularly suitable in reactions that have a strong silyl catalysis background and are hence not easily catalyzed by chiral Lewis acids. Possibly, such a non-enantioselective background reaction has hampered the development of a catalytic asymmetric version of the three-component coupling of aldehydes, carbamates, and allyltrimethylsilane.

We started our investigation by studying the three-component reaction of 2-naphthaldehyde (**1a**), benzyl carbamate (**2a**), and allyltrimethylsilane (**3**). An initial screening of different chiral acid motifs showed the phosphoric acid **5a** to be completely inactive (Table 1, entry 1).[6] N-trifyl phosphoramide **6a** was found to catalyze the reaction but in a low conversion, as well as with low enantioselectivity (entry 2). Chiral sulfonic acid **7a** proved to be much more active but provided no improvement in enantioselectivity (entry 3). As anticipated, the most promising results were indeed obtained

Table 1: Screening of different catalysts and reaction conditions.



Entry[a]	R	Catalyst	*t* [d]	Yield [%]	e.r.[b]
1	Cbz	**5a**	4	<1[c]	–
2	Cbz	**6a**	4	28[c]	59:41
3	Cbz	**7a**	1	95[c]	58:42
4	Cbz	**8a**	4	68	72:28
5	Boc	**8a**	4	17	38:62
6	CO_2Me	**8a**	4	90	63:37
7	Fmoc	**8a**	4	80	85:15
8	Fmoc	**8b**	10	40	52:48
9	Fmoc	**8c**	10	80	96:4
10	Fmoc	**8d**	4	82	93:7
11	Fmoc	**8e**	1.5	88	92:8

[a] Reactions were run with aldehyde (0.1 mmol), carbamate (0.15 mmol), allyltrimethylsilane (0.3 mmol), and catalyst (10 mol%) in $CHCl_3$ (1.0 M) at 18°C. [b] Determined by HPLC on a chiral stationary phase. [c] Determined by ^1H NMR spectroscopy using triphenylmethane as an internal standard. Boc = *tert*-butyloxycarbonyl, Cbz = carbobenzyloxy, Fmoc = 9-fluorenylmethyloxycarbonyl.

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with the chiral disulfonimide **8a** (entry 4), which formed the desired product with an enantiomeric ratio of 72:28.

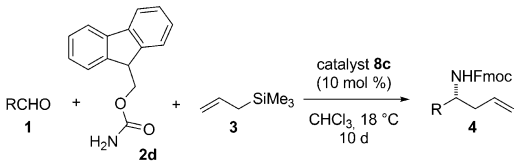
We next carried out screening of a series of carbamates. Both rate and enantioselectivity substantially varied with different carbamates. The reaction with *tert*-butyl carbamate (**2b**) furnished the desired product in only low yield and an enantioselectivity which was inferior to benzyl carbamate (Table 1, entry 5). The less bulky methyl carbamate (**2c**) reacted well and gave the corresponding product in a high yield but the enantioselectivity remained poor (entry 6). Continuing with our screening of carbamates, we then tested 9-fluorenylmethyl carbamate (Fmoc-NH_2; **2d**). Remarkably, this reagent has never been investigated, even in non-enantioselective three-component couplings with aldehydes and allyltrimethylsilane, despite the fact that it introduces a common protecting group. Encouragingly, the reaction with Fmoc-NH_2 showed an improvement in the enantioselectivity and gave the desired product with an enantiomeric ratio of 85:15 and in 80% yield (entry 7).

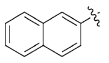
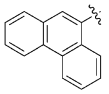
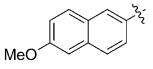
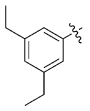
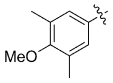
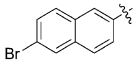
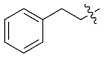
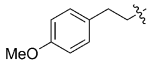
Having optimized the carbamate component, we focussed our attention towards modifying the aryl substituents at the 3,3′-position of the disulfonimide catalyst. Catalyst **8b**, which has recently been reported by our group as an efficient catalyst for hetero-Diels–Alder reactions of aldehydes gave inferior results compared to catalyst **8a** (compare entries 7 and 8 in Table 1). This suggested to us that bulky substituents at the 3,5-positions of the aryl groups are detrimental to both reactivity and enantioselectivity of the reaction. Learning from this result, we next tested catalyst **8c**, bearing only a single CF_3 substituent at the 4-position of the 3,3′-aryl groups. To our delight, this catalyst proved to be highly enantioselective and furnished the desired product with an enantiomeric ratio of 96:4 in a yield of 80% upon isolation (entry 9). We also synthesized the corresponding nitro-substituted catalyst **8d**, which, however, formed the product with slightly lower enantioselectivity (entry 10). Also, a decreased enantioselectivity was observed with the more active catalyst **8e** bearing additional fluorine substituents at the 3,5-positions (entry 11). Considering all these results, disulfonimide **8c** was chosen as the optimal catalyst.

We then set out to evaluate the substrate scope for our new direct asymmetric three-component reaction. Aromatic aldehydes formed the corresponding homoallylic amines in high yields and high enantiomeric ratios (Table 2, entries 1–6). Substituted naphthaldehydes containing electron-donating as well as electron-withdrawing substituents in the 6-position served as suitable substrates and furnished the products in high yields and enantioselectivities (entries 3 and 6). Also, 9-phenanthrene carboxaldehyde could be employed as the substrate and the corresponding homoallylic amine was isolated with an excellent enantiomeric ratio of 98.5:1.5 and a yield of 70% (entry 2). A *meta*-substituted benzaldehyde as well as benzaldehyde bearing substituents at both the *meta* and *para*-positions also delivered the corresponding products in high yields and enantioselectivities (entries 4 and 5). Gratifyingly, even aliphatic aldehydes could be converted into the corresponding homoallylic amines under these reaction conditions (entries 7–11). For example, hydrocinnamaldehyde gave the corresponding product in an excellent enantiomeric ratio of 96:4 and a yield of 71% (entry 7). *p*-Methoxy hydrocinnamaldehyde reacted similarly (entry 8). β-branched aliphatic aldehydes were also well tolerated and formed the corresponding products in high yields and good enantioselectivities (entries 9 and 10). Even an α-branched aliphatic aldehyde (isobutyraldehyde) could be used as substrate and gave the corresponding product in good yield and enantioselectivity (entry 11).

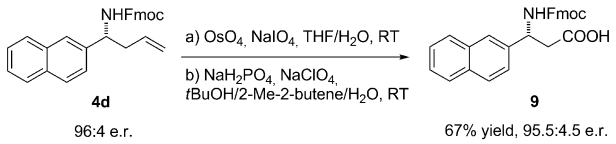
To further demonstrate the synthetic utility of our methodology, the product **4d** was oxidatively converted into the enantioenriched β^3-amino acid **9** (Scheme 1). β-Amino acids[7] such as derivative **9** are important motifs which serve as precursors for β-lactams, are constituents of several medicinally important compounds,[8] and most importantly, serve as monomers in the synthesis of peptidomimetic β-

Table 2: Substrate scope.



Entry[a]	R	Product	Yield [%]	e.r.[b,c]
1		**4d**	80	96:4
2		**4e**	70	98.5:1.5
3[d,e]		**4f**	84	95.5:4.5
4		**4g**	66	94:6
5		**4h**	84	92:8
6[d,e]		**4i**	80	95:5
7[f]		**4j**	71	96:4
8[f]		**4k**	70	94:6
9[e,g]		**4l**	83	92.5:7.5
10[e,g]		**4m**	78	92:8
11[g]		**4n**	65	91:9

[a] Unless noted otherwise, all reactions were run with aldehyde (0.1 mmol), Fmoc-NH_2 (0.15 mmol), allyltrimethylsilane (0.3 mmol), and catalyst (10 mol%) in $CHCl_3$ (1.0 M) at 18°C for 10 d. [b] Determined by HPLC on a chiral stationary phase. [c] For determination of absolute configuration, see the Supporting Information. [d] Reaction at 15°C. [e] Reaction was run for 12 d. [f] Used 0.3 mmol of Fmoc-NH_2 and 0.6 mmol of allyltrimethylsilane. [g] Used 0.6 mmol of allyltrimethylsilane.

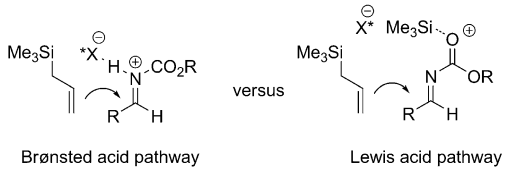


Scheme 1. Synthesis of the enantioenriched β-amino acid **9**.

peptides.[9] Especially, the N-Fmoc-protected β-amino acids are commonly applied in solid-phase peptide synthesis.

Compound **4d** was oxidized with $NaIO_4$ in the presence of a catalytic amount of OsO_4 to form the corresponding aldehyde, which without purification was further oxidized to furnish the desired Fmoc-protected β-amino acid **9** with an overall yield of 67% and without any loss in optical purity (Scheme 1). The enantiomer of **9** has recently been used in the solid-phase synthesis of a peptide hydroxamate, which is highly potent for the inhibition of an insulin-degrading enzyme (IDE) and is thus effective for the treatment of diabetes.[10]

Concerning the mechanism of our new asymmetric three-component reaction, we envision two distinct pathways (Scheme 2). Accordingly, the disulfonimide itself may act as a Brønsted acid which activates the in situ generated imine by



Scheme 2. Plausible catalytic pathways.

protonation. Alternatively, the catalyst may be silylated in situ from the allylsilane as shown before.[4a] This catalyst species in turn may activate the imine by silicon-based Lewis acid catalysis. Preliminary experiments utilizing a preformed imine and the preformed silylated catalyst gave nearly identical enantioselectivity as that obtained in the corresponding three-component reaction (see the Supporting Information). We therefore currently tend towards the Lewis acid catalysis pathway. However, further studies are clearly needed to confirm this notion.

In summary, we have developed the first catalytic asymmetric three-component synthesis of chiral homoallylic amines starting directly from aldehydes, carbamates, and allyltrimethylsilane. The use of readily available, inexpensive, and nontoxic starting materials is an attractive feature of our method. Moreover, the products bear the Fmoc substituent as a synthetically useful protecting group and can be readily converted into the corresponding Fmoc-protected β^3-amino acids. Importantly, both aromatic and aliphatic aldehydes can be converted into the corresponding homoallylic amines in high yields and enantioselectivities. With the successful development of this protocol, we present the first application of chiral disulfonimide in the activation of imines. Further work towards expanding the scope of the electrophiles which can be used in our chiral disulfonimide-based Lewis acid catalysis, and towards the design of even more enantioselective and active catalysts is currently ongoing in our laboratories.

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