Highly enantioselective organocatalytic formation of a quaternary carbon center *via* chiral Brønsted acid catalyzed self-coupling of enamides†

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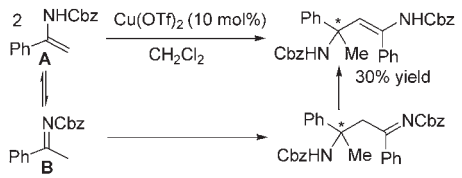
The enantioselective BINOL-phosphate catalyzed formation of a quaternary carbon center, bearing a *N*-atom has been achieved through the self-coupling reaction of enamides; the corresponding products have been isolated in up to >99% ee and their application for the synthesis of versatile synthetic building blocks—β-aminoketones—has been demonstrated.

The central task in the synthesis of organic compounds, simple or complex, is the construction of C–C bonds. Stereoselective C–C bond forming reactions are of particular interest for the preparation of enantiopure complex natural products and pharmaceutically important compounds. While tremendous progress has been made in developing methods for enantioselective generation of tertiary carbon centers, the enantioselective construction of quaternary carbon centers, and in particular, those bearing a nitrogen or other heteroatom, is still one of the most challenging tasks in organic chemistry.[1]

Recently, Kobayashi and co-workers have reported that enamides and enecarbamates can be used as nucleophiles, reacting with several electrophiles in the presence of metallic Lewis acids.[2] Furthermore, it was found that enamides and enecarbamates could undergo a self-coupling reaction on treatment with a strong Brønsted or Lewis acid such as TfOH, $Sc(OTf)_3$, or $Cu(OTf)_2$, which indicated, that an equilibrium between enamide **A** and ketimine **B** existed under acidic conditions (Scheme 1).[2a,e]

This reaction has apparently not been further investigated. However, this transformation is very suitable for the generation of quaternary stereocenters with nitrogen-containing substituents. These compounds could potentially be used as precursors for the synthesis of unnatural α-substituted α-amino acids through oxidative cleavage of the double bond, as synthetic intermediates for the preparation of chiral diamines through hydrogenation, or for β-aminoketones *via* acidic hydrolysis of their imine intermediates. In particular, β-aminoketones, and their derivatives have many attractive applications, for example in the area of pharmaceutical products,[3] as well as in polymer chemistry[4] with respect to paints and surface active agents.

This motivated us to develop an enantioselective version of the self-coupling reaction of enamides using chiral Brønsted acid organocatalysts.[5] Recently, the research groups of Akiyama[6] and Terada[7] independently developed BINOL-phosphates



Scheme 1 Self-condensation of enecarbamates.

as Brønsted acid organocatalysts for several enantioselective C–C bond-forming reactions, including the aza-ene-type reaction of *N*-benzoylimines with enecarbamates giving products with tertiary carbon centers.[7d] Later, several research groups,[8–10] notably the groups of Rueping[8] and List,[9] reported the application of BINOL-phosphates in the development of different highly enantioselective transformations. In most cases the key aspect of catalysis is the bifunctional character (Lewis acid/Lewis base) of the phosphoric acid moiety.[6b,e,7c,d] Terada and Sorimachi,[7f] and Zhou[10d] and co-workers have recently demonstrated that enamides (or enecarbamates) readily isomerize to imines under the influence of bifunctional BINOL-derived phosphoric acids and can be utilized as electrophilic components in Friedel–Crafts reactions.

We therefore expected that chiral BINOL-phosphates will facilitate the above mentioned equilibrium between enamide **A** and ketimine **B** (Scheme 1) and catalyze the subsequent enantioselective C–C bond forming reaction.

Herein we successfully realize this anticipation, and report a highly enantioselective (85–99% ee) formation of quaternary carbon centers through self-coupling of different enamides, catalyzed by chiral BINOL-phosphate.

Our studies commenced with the screening of chiral phosphoric acid catalysts ((*R*)-**1a–e**), easily prepared according to known procedures,[6–9] and bearing various types of substituents at the 3,3′-position on the binaphthyl backbone, for the self-coupling reaction of **2** in toluene at room temperature (Table 1, entries 1–5).

While an almost racemic mixture was obtained in 68% yield with catalyst (*R*)-**1a**, 56% ee and similarly good yield (70%) was observed for product **3** when 3,3′-phenyl-substituted BINOL-phosphate (*R*)-**1b** was used (Table 1, entries 1 and 2). Intriguingly, much higher enantioselectivity (96% ee, entry 3) was obtained applying catalyst (*R*)-**1c**, which contains a nitro group in the *para*-position of the 3,3′-phenyl-substituent of BINOL-phosphate. This indicates that both the steric and electronic properties of 3,3′-substituents are crucial for achieving high enantioselectivity. Notably, the phosphoric acid catalysts (*R*)-**1d** and (*R*)-**1e** with too sterically demanding 3,3′-substituents gave

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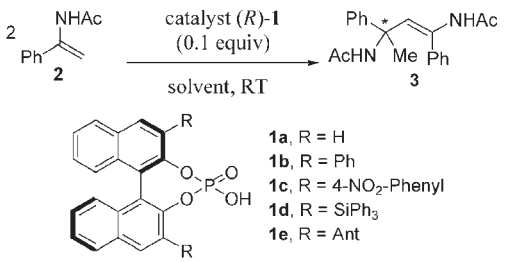
Table 1 Optimization of reaction conditions



Entry	Catalyst	Solvent	t/h	Yield (%)[a]	ee (%)[b]
1	**1a**	Toluene	72	68	4
2	**1b**	Toluene	72	70	56
3	**1c**	**Toluene**	**72**	**79**	**96**
4	**1d**	Toluene	72	Trace	9
5	**1e**	Toluene	72	12	25
6	**1c**	$CHCl_3$	72	66	96
7	**1c**	Toluene	24	56	97
8	**1c**	CH_3CN	24	—	—
9	**1c**	THF	24	>9	96
10	**1c**	Diethyl ether	24	>14	96
11	**1c**	CH_2Cl_2	24	64	95

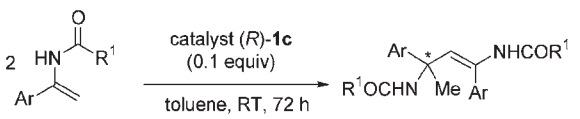
[a] Yield of isolated product after column chromatography on SiO_2. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralcel OD) in comparison with authentic racemic material.

only very low yields (up to 12%) and enantioselectivities (up to 25% ee) (Table 1, entries 4 and 5).

Further solvent-screening studies with the selected catalyst (*R*)-**1c** (Table 1, entries 6–11) demonstrated, that toluene, initially chosen, also proved to be the optimal solvent under the reaction conditions used.

Self-coupling of various enamides was then investigated using (*R*)-**1c** as the catalyst in toluene (Table 2). The effect of substituents in the aromatic ring of the enamide on the reactivity and enantioselectivity was first examined. Whereas either no conversion or only low yield (up to 15%, entries 2 and 3 *vs.* entry 1) was observed for enamides, which contain electron-withdrawing groups in the *ortho*- or *meta*-position in the aromatic ring, similarly good yields, 82 and 83%, respectively,

Table 2 Asymmetric self-coupling of enamides by using BINOL-phosphate (*R*)-**1c**



Entry	R^1	Ar	Yield (%)[a]	ee (%)[b]
1	Me	C_6H_5	79	96
2	Me	2-ClC_6H_4	—	—
3	Me	3-ClC_6H_4	15	88
4	Me	4-ClC_6H_4	82	>99[c]
5	Me	4-$MeOC_6H_4$	83	88
6	Et	C_6H_5	70	85
7	Pr	C_6H_5	35	97
8	Pr	4-ClC_6H_4	63	>99

[a] Yield of isolated product after column chromatography on SiO_2. [b] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material. [c] $[\alpha]_D^{25} = -365$ (c = 0.1, CH_2Cl_2).

were obtained for enamides bearing electron-withdrawing or electron-donating groups in the *para*-position of the aromatic ring (entries 4 and 5). These results clearly demonstrate that steric, rather than electronic properties, influence the reactivity of substrates in this BINOL-phosphate catalyzed reaction.

Further exploration concentrated on the enamide protecting group, as it was expected also to influence the reaction reactivity. We indeed found that the bulkiness of R^1 in the *N*-protecting group effected the reactivities: the larger the R^1, the lower the yield (Table 2, entry 1 *vs.* 6 and 7; entry 4 *vs.* 8). These results can be rationalized by the fact that the bulky substituents impair the approach of the substrate to the 3, 3′-substituted (*R*)-BINOL-phosphate **1c**, resulting in lower conversion rates. Notably, in all cases, the products were obtained with high enantiomeric excess of 85–99% (Table 2).

Based on the experimental results and reported mechanistic assumptions for different transformations catalyzed by BINOL-phosphates,[6–10] we postulate the mechanism of the self-coupling reaction (Fig. 1). In this sequence, the first step (Fig. 1a) concerns the equilibrium between enamide and ketimine forms in the presence of a chiral Brønsted acid. The next steps (Fig. 1b) cause a coupling reaction, due to the dual function of the phosphoric acid group. While the formed *N*-acyl-ketimine can easily be protonated through the Lewis acidic part of the phosphoric acid moiety to form an iminium cation intermediate as a good electrophile (as it has already been reported by Terada and co-workers for aza-ene-type reaction[7d]), the NH group of the enamide (nucleophile), can form an NH···O hydrogen bond with the Lewis basic phosphoryl oxygen atom. Following this tight ion pair formation, a subsequent bond recombination and release of chiral BINOL-phosphate results in the desired product.

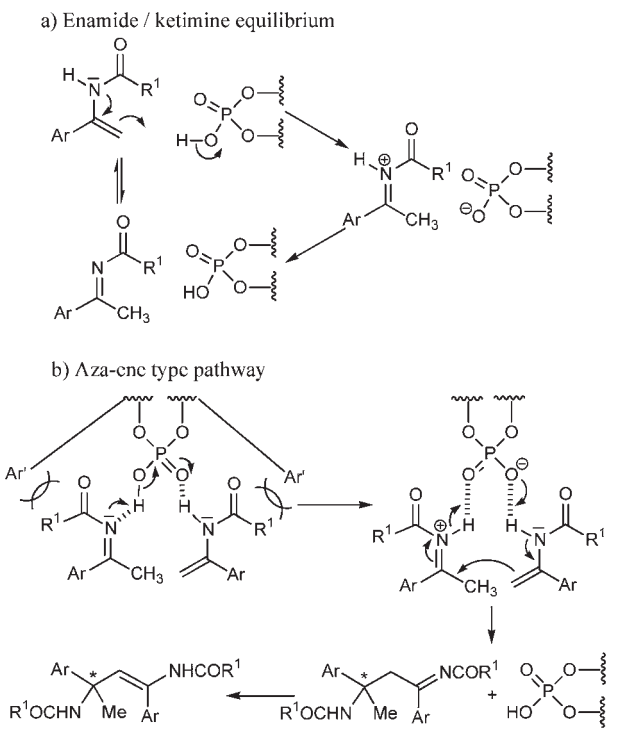
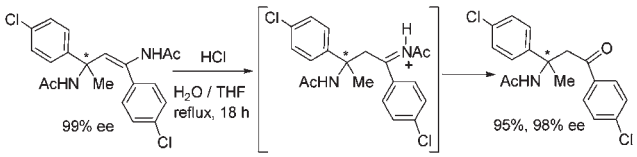


Fig. 1 A plausible mechanism for the self-coupling reaction of enamides leading to a quaternary carbon center.



Scheme 2 Conversion to β-aminoketone with the quaternary carbon center bonded to nitrogen.

According to the proposed mechanism, 3,3′-substituents of the BINOL-phosphate catalyst might have unfavourable steric interactions (Fig. 1b) with the bulky R^1 group (*e.g.* Et, Pr), and with the substituents at the *ortho*- or *meta*-position in the aromatic ring of the enamide, and therefore could account for the outcome of the reaction described above (Table 2).

Considering the ubiquity of chiral amines, where the nitrogen is adjacent to quaternary carbon atoms, application of the asymmetric self-coupling reaction of enamides to the synthesis of useful chiral target molecules, *e.g.* β-aminoketones, is envisioned.

Notably, while various synthetic routes to different enantiomerically pure β-aminoketones with tertiary carbon centers have been developed in recent years (the most widespread of which is based on the Mannich reactions),[11] the reports on asymmetric synthesis of β-aminocarbonyl compounds with quaternary carbon bearing a nitrogen atom are scarce and restricted to the synthesis of derivatives containing the geminal amino and fluoroalkyl groups.[12]

Here we demonstrate, for the first time, that the present self-coupling reaction of enamides could successfully be applied to the synthesis of potentially useful synthetic building blocks—β-alkyl-β-aminoketones. (Scheme 2). Treatment of the selected adduct (with 99% ee) of the self-coupling reaction with 2N HCl in H_2O–THF provided the corresponding β-methyl-β-aminoketone ($[\alpha]_D^{25} = -22$; $c = 0.1$, CH_2Cl_2) in 95% isolated yield and 98% ee (Scheme 2).

In summary, we have successfully developed a highly enantioselective Brønsted acid catalyzed self-coupling reaction of enamides providing quaternary carbon bearing a nitrogen atom and demonstrated its application for asymmetric synthesis of useful synthetic intermediates—β-methyl-β-aminoketones.

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