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Enantioselective Functionalization of Enamides at the β-Carbon Center with Indoles

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Abstract

We report an enantioconvergent approach for the functionalization of enamides at the β-carbon atom, which involves a chiral Brønsted acid induced tautomerization of 2-amidoallyl into 1-amidoallyl cations. These putative reactive intermediates were produced by ionization of racemic α-hydroxy enamides with a chiral Brønsted acid and captured with substituted indoles in a highly regio- and enantioselective manner.

Keywords

2-amidoallyl cations; asymmetric catalysis; Brønsted acids; indoles; tautomerization

The development of new reactions that construct stereocenter-containing organonitrogen compounds is highly valued owing to the ubiquity of nitrogen atoms in bioactive molecules, such as natural products and pharmaceuticals.[1] In recent years, a particular problem that has garnered attention is the catalytic enantioselective synthesis of functionalized enamides at the β-carbon atom, which is approached through conjugate addition to α,β-unsaturated imides (Scheme 1).[2] This is a non-trivial undertaking because as opposed to the well-established carbonyl or nitro variations,[3] α,β-unsaturated imides are typically less reactive as Michael acceptors, and there are only limited examples of their reactivity. One of the earliest methods was reported by Carretero and co-workers,[2a] who demonstrated that the addition of dialkylzinc reagents to the β-carbon atom could be accomplished by using copper(I) and chiral phosphoramidite complexes as the source of asymmetric induction. In the ensuing years, the groups of Palacios,[2b,c] Zezschwitz,[2d] and Kobayashi[2e] reported their variants of these copper-catalyzed reactions. Along this line of work (**1a**→**1b**), Pedro and co-workers showed that lanthanum(III) and chiral PyBOX ligands could also be employed to catalyze the conjugate addition of malonate esters to α,β-unsaturated imides.[2f]

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Conflict of interest

The authors declare no conflict of interest.

With the rapid advancement of asymmetric organocatalysis, some precedents on the utility of this approach to furnish b-functionalized enamides have naturally emerged. For instance, the groups of Smith[2g] and Pericas[2h] reported that the activation of nucleophiles with chiral benzotetramisoles enabled enantioselective conjugate additions to the β-carbon atom, which were followed by intramolecular annulation (**2a**→**2c**). In the arena of chiral Brønsted acid catalysis, the groups of Bandini[2i] and Toste[2j] disclosed that nucleophilic capture of α,β-unsaturated iminium ions **3b**, generated in situ upon protonation of allenamides **3a**, could be performed in an enantioselective manner. However, the new stereocenter in these examples was only formed within the newly incorporated nucleophiles, but not at the intended β-carbon atom of the enamide adducts **3c**.

To advance this underdeveloped area, we herein describe a novel enantioconvergent synthesis of β-functionalized enamides, starting from racemic α-hydroxy enamides (**4**).[4] We envisioned that stereoablative ionization of this starting material with a chiral Brønsted acid should produce unsymmetric 2-amidoallyl cation **5a**.[5] In the presence of the readily dissociated triflate counteranion, this intermediate has been shown to undergo nucleophilic capture exclusively at the less substituted α′-carbon atom to furnish α′-functionalized enamides 6.[6] Inspired by this work, we proposed that the activation of substrate **4** with a chiral Brønsted acid invokes a much tighter ion-pair interaction[7] between the emerging 2-amidoallyl cation and the bulky chiral anion. This critical intermolecular force could consequently introduce substantial steric congestion, thus rendering an attack at the a'-carbon atom kinetically unfavorable. In the absence of nucleophilic capture, it is conceivable that an alternative reaction process involving 2-amidoallyl cations could competitively occur considering their presumed high reactivity. An example of such hypothetical events might involve a proton transfer cascade that would tautomerize 2-amidoallyl cation **5a** into the thermodynamically more stable 1-amidoallyl cation **5b** under the reaction conditions.[8a] Inherently, this newly formed reactive species could interact with the chiral catalyst through the formation of a contact ion pair. This chiral environment would provide facial differentiation towards nucleophilic addition, which should occur at the distal, sterically more accessible β-carbon atom to furnish enantiomerically enriched enamide **7**.

Our proof-of-concept experiments are summarized in Table 1.[10] Using racemic α-hydroxy enamide (±)-**8**,[6] we began by screening a series of BINOL- and VAPOL-derived phosphoric acids **11a–11g**. Ionization of this model substrate with these catalysts in the presence of indole and 4 Å molecular sieves in dichloromethane at room temperature indeed led to preferential functionalization at the β-carbon atom to give (+)-**10** as the major product (entries 1–7). Interestingly, use of the 9-phenanthryl-substituted catalyst **11d** yielded a promising e.r. of 79:21. Encouraged by this result, we then evaluated various non-polar solvents that are commonly employed in chiral Bronsted acid catalyzed transformations (entries 8–12), and found that performing our reaction in dichloroethane substantially improved the enantioselectivity. In fact, β-indolyl enamide (+)-**10** was isolated with 88:12 e.r.

To further maximize asymmetric induction, the reaction temperature was subsequently modulated. Lowering the reaction temperature to 4°C and −10°C not only improved the enantiomeric ratio to 92:8 and 93:7, respectively, but also favorably shifted the

regioselectivity towards the β-carbon atom (entries 12–14).[11] These results could be further enhanced by diluting the reaction mixture, but at the cost of a longer reaction time (entries 14–16). The significance of the addition of 4 Å molecular sieves to capture the water byproduct generated upon ionization is showcased by entry 17 as the absence of such additives promoted the formation of a side product that was chromatographically inseparable from the desired β-indolyl enamide (+)-**10**.

Scheme 2 depicts our evaluation of the indole scope. To this end, substrate (±)-8 was activated with 10 mol% of catalyst **11d** in the presence of 4 Å molecular sieves at −10°C in dichloroethane at a concentration of 0.1M based on the starting material. The use of electron-rich 5-methoxyindole as well as halogenated 5-bromoindole and 6-chloroindole furnished the corresponding β-indolyl enamides (+)-**12a–12c** in good yields with excellent regio- and enantioselectivity, including 99:1 e.r. for (+)-**12c**. An attempt to increase the scale of the reaction with 5-bromoindole to a one-gram process was also fruitful as the resulting product (+)-**12b** was isolated in 83% yield with 92:8 e.r. as a single regioisomer. The suitability of several electron-deficient indoles, such as methyl indole-5-carboxylate, 5-nitroindole, and 4-cyanoindole, was also examined. Overall, these nucleophiles proved to be well tolerated in this reaction as the corresponding enamides (+)-**12d–12** f were isolated in good yields with excellent enantiomeric purity. Furthermore, these products were isolated as single regioisomers.

We also investigated sterically encumbered nucleophiles, such as 5-methoxy-1*H*-benzo[*g*]indole. While the resulting enamide (+)-**12g** was afforded in 59% yield with 91:9 e.r., a considerable erosion in regioselectivity was surprisingly noted. Interestingly, with 2-phenylindole, the resulting enamide (+)-**12h** was produced in 64% yield as a single regioisomer, but a lower asymmetric induction was observed. Finally, we tested *N*-methyl- and **N**-benzylindoles, which revealed that protected indoles are not suitable for this reaction. In fact, the enamide adducts (+)-**12i** and (+)-**12j** were both obtained in lower yields with reduced enantiomeric ratios.

As shown in Scheme 3,[12] our studies continued with an evaluation of the substituent effects using a series of racemic α-hydroxy enamides (±)-**13** as starting materials.[13] Starting with aryl substituents such as phenyl and tolyl, the reactions produced β-indolyl enamides (+)-**14a–14c** in good yields and enantioselectivity. However, the regioselectivity was fairly modest with these activated substrates. Intriguingly, an exquisite control of selectivity was regained when a 4-fluoro- or a 4-chlorophenyl substituent was incorporated into the substrate. In fact, the corresponding halogenated products (+)-**14d** and (+)-**14e** were isolated essentially as a single isomer in terms of both regioisomeric and enantiomeric purity. As we explored the aliphatic series, substrates that were decorated with straight-chain alkyl and allyl groups were generally tolerated under the reaction conditions to exclusively afford the β-addition products (+)-**14 f**–**14i** in good yields and enantiomeric ratios; however, a lower e.r. of 87:13 was observed for the α-allyl substrate. Unsurprisingly, this reaction appeared to be sensitive to steric effects as both the enantiomeric purity and yield dropped when a bulky isobutyl group was installed at the α-carbon atom in (+)-**14j**. A bulky substituent at the nitrogen center also affected the efficacy of the asymmetric induction as evidenced by the formation of the *N*-butyl β-indolyl enamide adduct (+)-**14k** in poor enantioselectivity.

To account for the observed stereochemical outcome, we propose a possible mode of activation (**15**; Scheme 4). This transition model is based on a contact ion pair interaction[7] between the chiral catalyst and the 1-amidoallyl cation in its most stable iminium-type conformation, which involved minimization of 1,3-allylic strain between the substituent at the α-carbon atom and the sterically demanding *N*-tosyl group.[8b] Following a model that was proposed by Bandini,[2i] the N-H moiety of the indole was believed to play a significant role towards regulating the enantioselectivity, presumably via a hydrogen bond to the chiral anion.[14] This premise was clearly supported by the lack of enantioenrichment when protected indoles were subjected to the reaction ((+)-**12i** and (+)-**12j**).

In summary, we have described an unprecedented chiral Brønsted acid catalyzed enantioconvergent synthesis of β-substituted enamides. Mediated by tautomerization of transient 2-amidoallyl cations upon ionization of racemic α-hydroxy enamides, the key 1-amidoallyl cation intermediates were captured by indoles at the distal β-carbon atom in an enantioselective manner. Further expansions of this method, mechanistic investigations, and applications towards complex molecule synthesis are currently ongoing in our laboratory. The results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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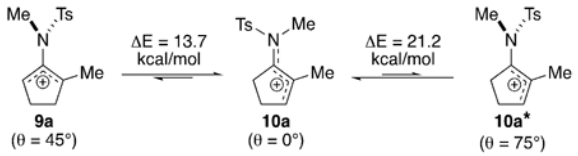
[8]. Using the b3lyp/6–31 + g(d) basis set, DFT calculations revealed that the 1-amidoallyl cation 10a is more stable than 2-amidoallyl cation 9a by 13.7 kcalmol−1;the dihedral angles (θ) of the C-N axis of these intermediates in the ground-state conformations were found to be 45° for 9a and 0° for 10a whereas the highest-energy conformation of 10a was located for θ = 75° with a cost of 21.2 kcalmol−1. See the Supporting Information for details.



[9]. The preferred conformation of the C-N axis in the solid state and the absolute stereochemistry of the β-carbon atom were assigned by analogy to X-ray structures of (+)-12c, (+)-14a, and (+)-14b. Nonetheless, there appears to be free rotation about the C-N axis in these products in solution based on NOE observations. See the Supporting Information. CCDC 1842375, 1589611, and 1589612 ((+)-12c, (+)-14a, and (+)-14b) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[10]. See the Supporting Information for detailed reaction optimization.

[11]. The reaction failed to proceed below −10°C.

[12]. These substrates failed to react under the ionization conditions listed in Scheme 2. See the Supporting Information for reaction optimization.

[13]. Six-membered-ring substrates did not react under these conditions, and further investigations are currently ongoing. Mac-Millan and co-workers also observed a similar behavior in their enantioselective organocatalytic reaction with oxyallyl cations; see:Liu C, Oblak EZ, Vander Wal MN, Dilger AK, Almstead DK, MacMillan DWC, J. Am. Chem. Soc 2016, 138, 2134–2137. [PubMed: 26797012]

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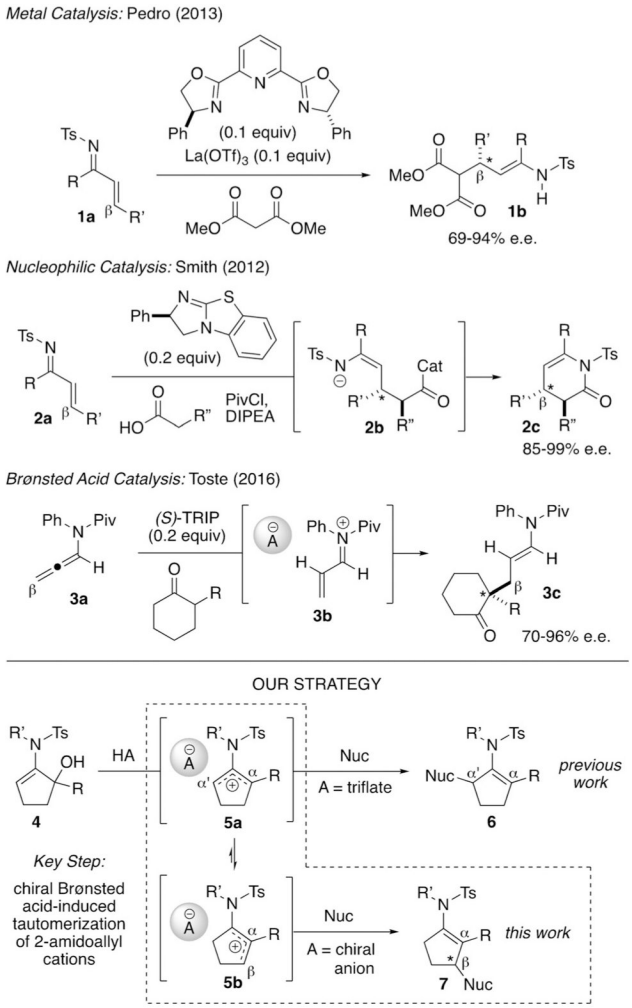
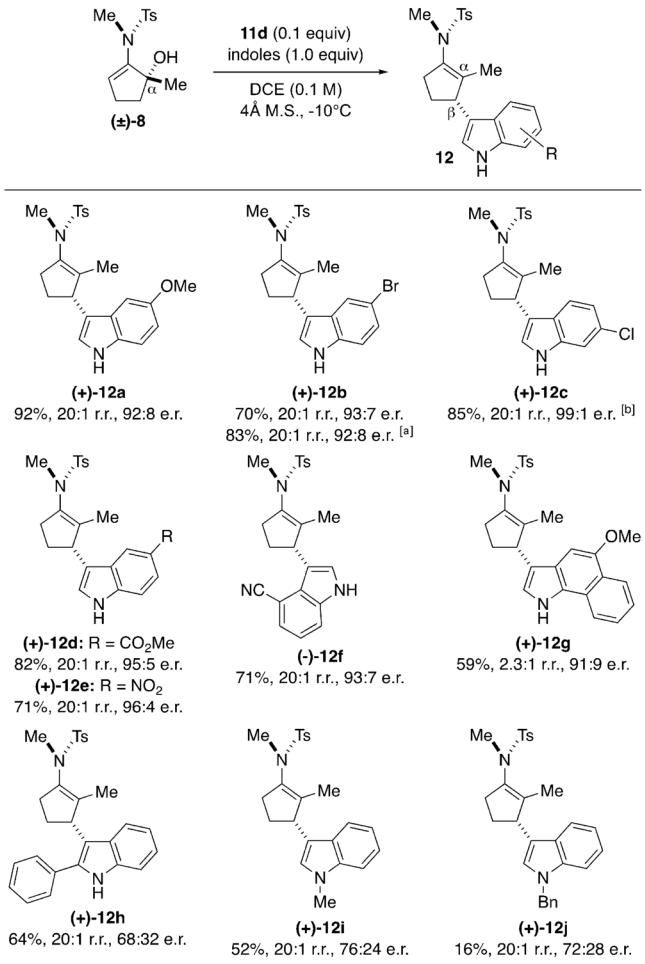


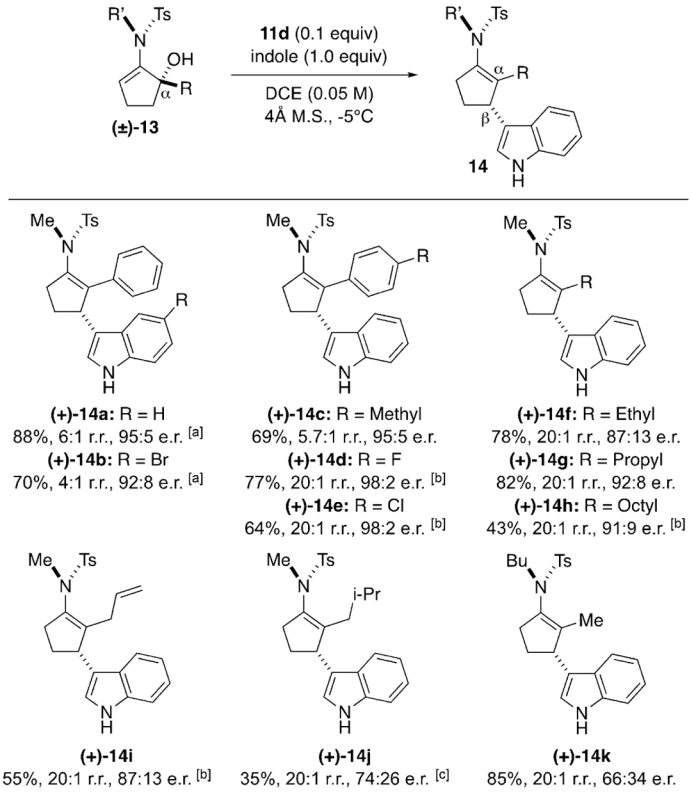
Scheme 1.

Representative strategies towards the enantioselective β-functionalization of enamides. DIPEA= diisopropylethylamine, Nuc= nucleophile, PivCl= pivaloyl chloride, Ts =tosyl.



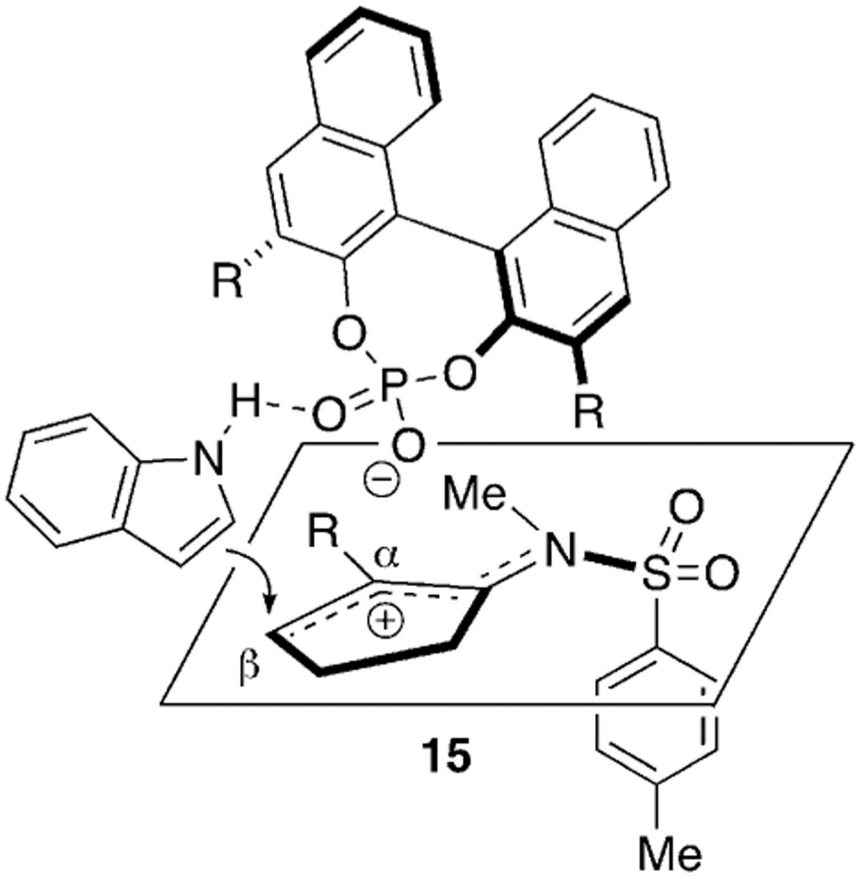
Scheme 2.

Indole scope.[9] Combined yields of both regioisomers after flash column chromatography are given. The regioisomeric ratios were determined by ^{1}H NMR analysis. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [a] Reaction performed on one-gram scale. [b] Structure determined by X-ray crystallography.



Scheme 3.

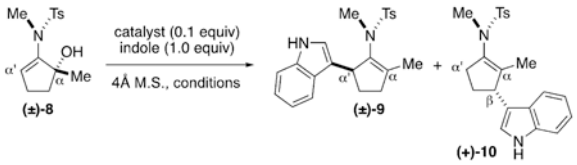
Substrate scope.[9] Combined yields of both regioisomers after flash column chromatography are given. The regioisomeric ratios were determined by ^{1}H NMR analysis. The enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [a] Structure determined by X-ray crystallography. [b] With 0.3 equiv of catalyst **11d** to improve the rate. [c] At a concentration of 0.1M.



Scheme 4.
A possible mode of activation.

Table 1:

Reaction optimization.[9]



Entry	Cat.	Solvent	Conc. [m]	*T* [°C]	*t* [h]	r.r.[a]	e.r.[b]	Yield [%][c]
1	**11a**	CH_2Cl_2	0.2	RT	40	1:3	52:48	76
2	**11b**	CH_2Cl_2	0.2	RT	42	1:4.3	53:47	53
3	**11c**	CH_2Cl_2	0.2	RT	24	1:4.3	58:42	74
4	**11d**	CH_2Cl_2	0.2	RT	15	1:4.3	79:21	70
5	**11e**	CH_2Cl_2	0.2	RT	40	1:5.7	52:48	76
6	**11f**	CH_2Cl_2	0.2	RT	40	1:5.7	56:44	63
7	**11g**	CH_2Cl_2	0.2	RT	24	1:5.3	48:52	74
8	**11d**	toluene	0.2	RT	15	1:6.1	72:28	44
9	**11d**	Bu_2O[d]	0.2	RT	38	1:7.3	68:32	49
10	**11d**	CCl_4	0.2	RT	16	1:2	64:36	46
11	**11d**	$CHCl_3$	0.2	RT	15	1:5.7	71:29	84
12	**11d**	DCE	0.2	RT	15	1:4.3	88:12	76
13	**11d**	DCE	0.2	4	14	1:6.7	92:9	74
14	**11d**	DCE	0.2	−10	63	1:7.3	93:7	68
15	**11d**	DCE	0.1	−10	48	1:8	94:6	77
16	**11d**	DCE	0.05	−10	65	1:13.3	94:6	73
17	**11d**	DCE[e]	0.1	−10	60	1:13.3	94:6	66[f]

[a]The regioisomeric ratios (r.r.) between (±)-**9** and (+)-**10** were determined by ^{1}H NMR analysis.

[b]The enantiomeric ratios (e.r.) were determined by HPLC analysis on a chiral stationary phase.

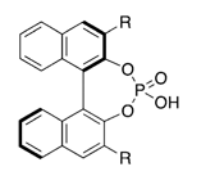
[c]Combined yields of both regioisomers after flash column chromatography.

[d]Catalyst **11d** did not fully dissolve in this solvent.

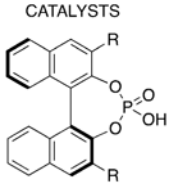
[e]Without 4 Å molecular sieves (M.S.).

[f]Contaminated with an inseparable side product.

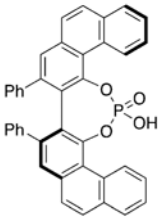
CATALYSTS



11a: R = H
11b: R = 3,5-$(CF_3)_2C_6H_3$
11c: R = 2,4,6-$(iPr)_3$-C_2H_6
11d: R = 9-phenanthryl



11e: R = Ph_3Si
11f: R = 9-anthracenyl



11g