Brønsted-Acid Catalyzed Diastereoselective Synthesis of Spiroisoindolinones from Enamides

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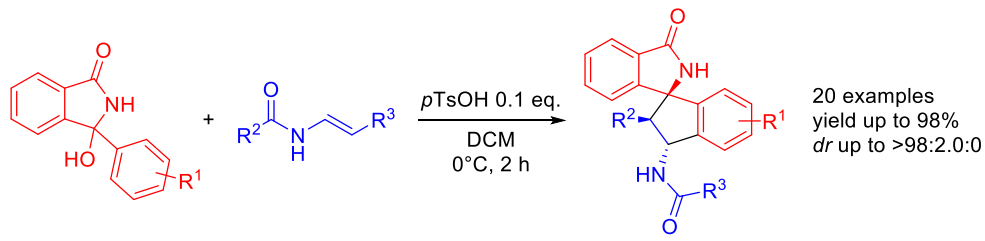


Abstract

A highly diastereoselective synthesis of spiroisoindolinones from enamides and 3-hydroxy-isoindolinones is reported. The reaction proceeds rapidly in the presence of *para*-toluenesulfonic acid as Brønsted acid-catalyst and affords a variety of densely substituted spiroisoindolinoes with three contiguous stereogenic centers in high yields (up to 98%) and diastereoselectivities (up to *dr* >98:<2:0:0).

Introduction

Nitrogen-containing heterocycles are of central importance in organic chemistry and constitute a prominent scaffold in natural products and active pharmaceutical ingredients.[1] Among different heterocyclic scaffolds, spirocyclic compounds are gaining increasing attention in medicinal chemistry and drug discovery,[2] particularly due to their intricate three-dimensional structures.[3] Spiro-fused

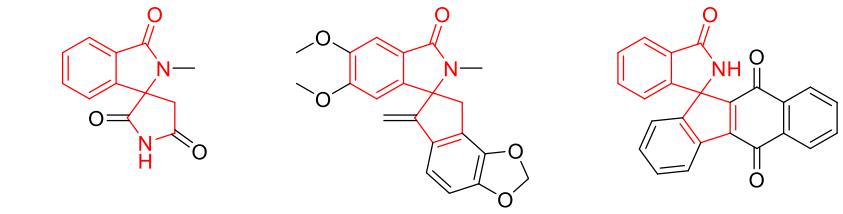
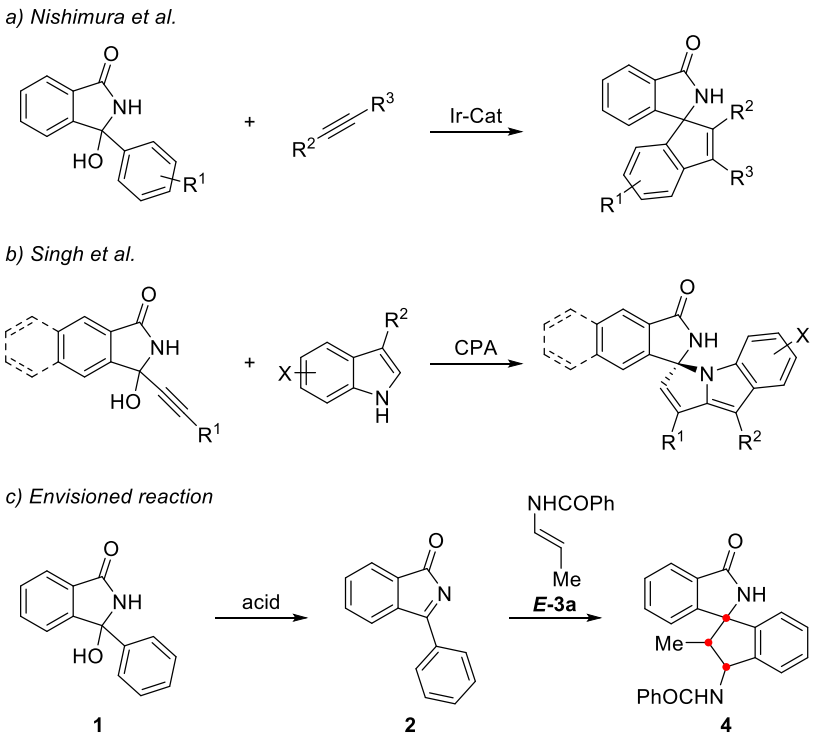


Figure 1: Selected examples of spiroisoindolinones.

isoindolinones form an important spirocyclic motif, which can be found in a variety of compounds with interesting biological activities (Figure 1).[4]

Therefore, several synthetic approaches towards the spiroisoindolinone framework have been developed over the last years.[5] According to the literature, 3-hydroxyisoindolinones are particularly suitable starting materials for the synthesis of spiroisoindolinones (Scheme 1). In three separate reports, the Nishimura group disclosed iridium-catalyzed annulation reactions with alkenes, alkynes or 1,3-enynes (Scheme 1a).[6] Singh and coworkers reported a chiral Brønsted acid catalyzed enantioselective synthesis of spiroisoindolinone-indolines via a formal [3+2]-cycloaddition of 3-alkynyl-substutited 3-hydroxyisoindolinones with indoles (Scheme 1b).[7] In all these reports, the formation of an electrophilic acylimine species **2** as first key intermediate is proposed. Our group has successfully exploited the addition of enamides to similar acylimine species as key step in the development of novel highly stereoselective transfromations.[8]

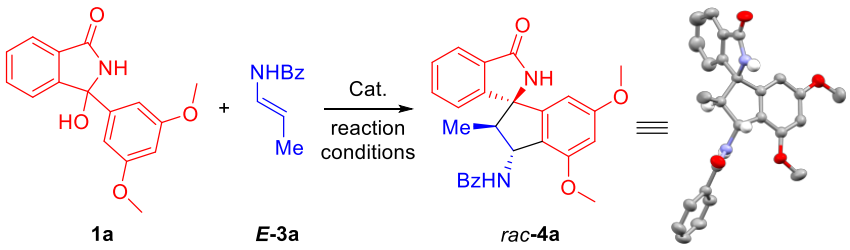
Scheme 1: Synthetic approaches towards spiroisoindolinones 4 from 3-hydroxyisoindolinones.



Recently, we were able to extend our methods towards the stereoselective synthesis of different heterocyclic scaffolds.[9] We envisioned, that enamides[10] should also undergo an analogous formal [3+2]-cycloaddition with in situ generated acylimine species of type **2**. This transformation would enable the rapid construction of amino-substituted spiroisoindolinones with three contiguous stereocenters as interesting scaffold in the context of medicinal chemistry (Scheme 1c).

To test the feasibility of our idea, we selected the reaction between the 3,5-dimethoxybenzene substituted 3-hydroxyisoindolinone **1a** and *E*-enamide ***E*-3a** as first model transformation (Table 1).[11,12] Gratifyingly, several Lewis and Bronstedt acids, such as $Sc(OTf)_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, TFA, $NHTf_2$ or *p*-TsOH, catalyzed the reaction efficiently, furnishing the desired spirocyclic product **4a** with three contiguous stereocenters in 49-93% yield and high levels of diastereoselectivity (entries 1-6).[13] *p*-TsOH was selected as catalyst of choice for further investigation, both due to the favorable reaction outcome (entry 6) and its low price and widespread availability. CH_2Cl_2 proved to be the optimal solvent for this transformation. Reactions in other solvents, such as THF, MeCN or $CHCl_3$, provided the spirocyclic product **4a** in slightly reduced yields of 65-85% and high diastereoselective, albeit only after prolonged reaction times (16 hours, entries 7-9). Protic solvents, e.g. MeOH, proved to be not suitable for this reaction (entry 10). Interestingly, the *p*-TsOH-catalyzed reaction proceeded efficiently even a 0 °C, furnishing spirocycle **4a** in 91% yield within two hours in an essentially diastereomerically pure form (entry 11). Decreased amounts of *p*-TsOH led to significantly reduced yields (entries 12 and 13).

Table 1: Optimization of the reaction conditions[a]



1a ***E*-3a** *rac*-**4a**

entry	catalyst	solvent	yield[b] [%]	*dr*[c]
1	$Sc(OTf)_3$	CH_2Cl_2	93	93:7:0:0
2	$Fe(OTf)_3$	CH_2Cl_2	85	93:7:0:0
3	$Cu(OTf)_3$	CH_2Cl_2	84	95:5:0:0
4	TFA	CH_2Cl_2	49	98:2:0:0
5	$HNTf_2$	CH_2Cl_2	85	74:26:0:0
6	*p*-TsOH	CH_2Cl_2	90	98:2:0:0
7	*p*-TsOH[d]	THF	68	>98:2:0:0
8	*p*-TsOH[d]	MeCN	85	95:5:0:0
9	*p*-TsOH[d]	$CHCl_3$	75	98:2:0:0

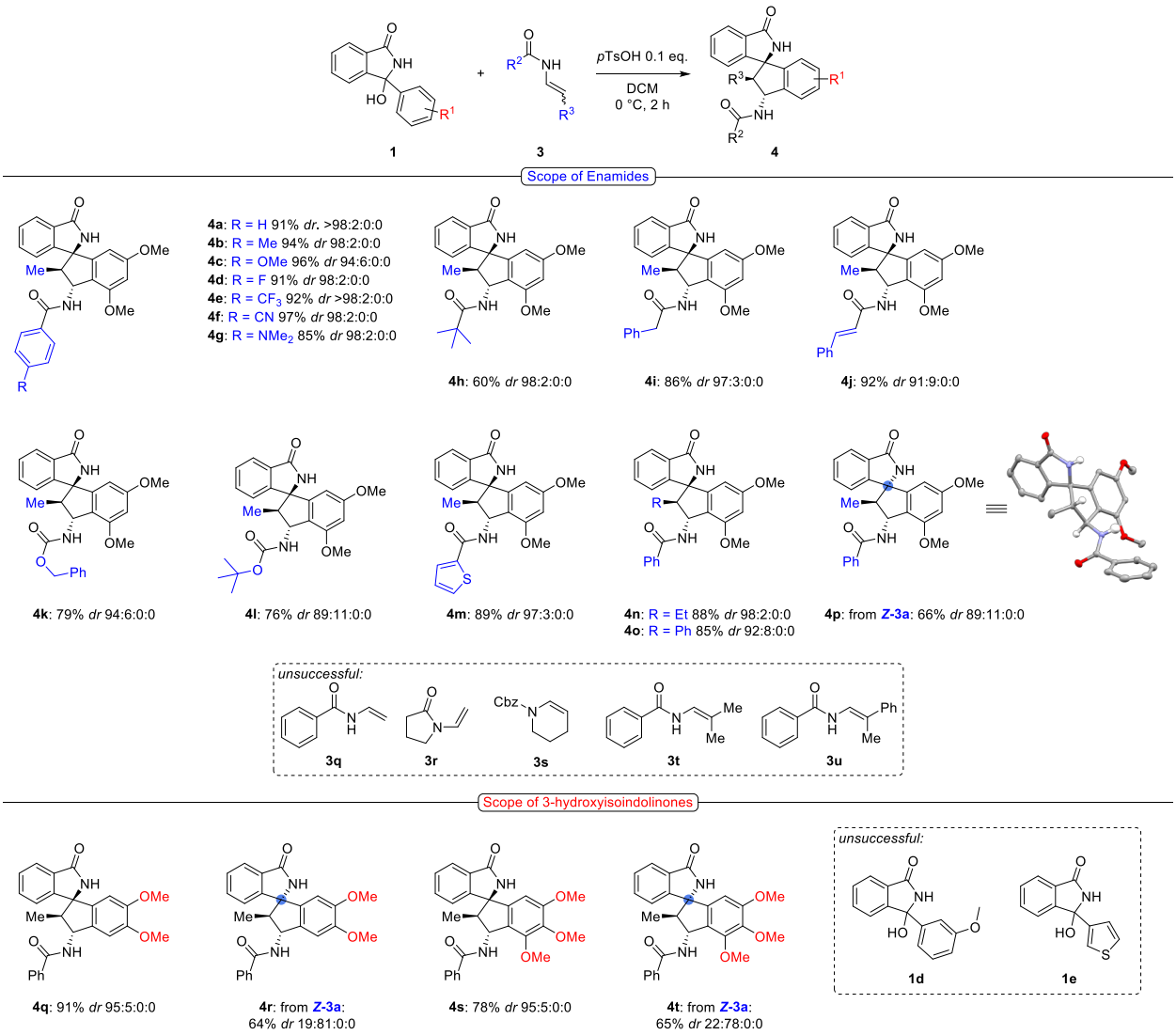
10	*p*-TsOH	MeOH	0	-
11	*p*-TsOH[e,d]	CH_2Cl_2	91	>98:2:0:0
12	*p*-TsOH[e,d,f]	CH_2Cl_2	73	96:4:0:0
13	*p*-TsOH[e,f]	CH_2Cl_2	61	95:5:0:0

[a] reaction conditions: 10 mol% catalyst, rt, 2 h. [b] Overall isolated yield of all diastereomers. [c] The reported diastereomeric ratio (*dr*) refers to the diastereomeric ratio of the crude reaction mixture as determined by ^{1}H NMR. [d] 16 h. [e] 0 °C. [f] with 5 mol% catalyst. [g] with 2.5 mol% catalyst. Structure of **4a** in the solid state (methyl and aromatic H atoms are omitted for clarity). Bz = benzoyl

Based on our optimization, the substrate scope was investigated with 10 mol% *p*-TsOH as catalyst in CH_2Cl_2 at 0 °C. Initially, the reaction of 3-hydroxyisoindolinone **1a** with a series of different enamides **3** was explored (Scheme 2). Different benzoyl-derived *E*-enamides **3a**-**3g** bearing electron-withdrawing or electron-donating groups afforded the desired spirocyclic products **4a**-**4g** in uniformly high yields (85-97%) and diastereoselectivities (*dr* ≥ 96:4:0:0) irrespectively of the electronic nature of the substituent. Reactions with different alkylamide derivatives **3h**-**3i** and the thiophene derivative **3m** furnished the spiro-isoindolinones **4h**, **4i**, and **4m** in 60-89% yield and high levels of diastereoselectivity. Transformation of a cinnamoyl-derived enamide **3j** afforded the spirocycle **4j** bearing an attached acrylamide moiety in 92% yield with high diastereoselectivity. Interestingly, reactions with enecarbmates **3k** and **3l** proceeded smoothly and the Cbz- and Boc-protected products **4k** and **4l** were obtained in 79 and 76% yield. In case of the Boc-derivative **4l** a slightly decreased level of diastereoselective was observed. Transformations with the ethyl or phenyl-substituted enamides **3n** and **3o** led to the corresponding spiroisoindolinones **4n** and **4o** in high yields and diastereoselectivities. By employing *Z*-enamide ***Z*-3a**, the corresponding 1,2-*trans* diastereomer **4p** could be synthesized in good yields and a diastereoselectivity of 90:10. Unfortunately, reactions with the unsubstituted enamide **3q**, enamides lacking a free NH-group (**3r** or **3s**) or bulkier enamides (**3t** or **3u**) did not proceed at all and only unreacted starting materials were observed even after prolonged reaction times.

Attempts to construct spiroisoindolinones from different 3-hydroxyisoindolinones had limited success. Only the two 3-hydroxyisoindolinones **1b** and **1c** bearing electron-rich di- or trimethoxybenezene residues underwent a formal [3+2]-cycloaddition with enamide ***E*-3a**, affording the desired spirocycles **4q** and **4s** in 91% and 78% yield. Again, reactions of *Z*-enamide ***Z*-3a** with the 3-hydroxyisoindolinone **1b** and **1c** afforded the corresponding 1,2-*trans*, 2,3-*trans*-configured spirocycles **4r** and **4t** as major diastereomer. In both cases yields and diastereoselectivties were slightly lower compared to reactions with the *E*-enamide ***E*-3a**. Reactions with 3-hydroxyisoindolinones **1d** and **1e** bearing a less electron-rich arene or heteroarene residue only led to decomposition of the starting materials.

Scheme 2: Substrate Scope of the Formal [3+2]-cycloaddition with different enamides and 3-hydroxyisoindolinones.

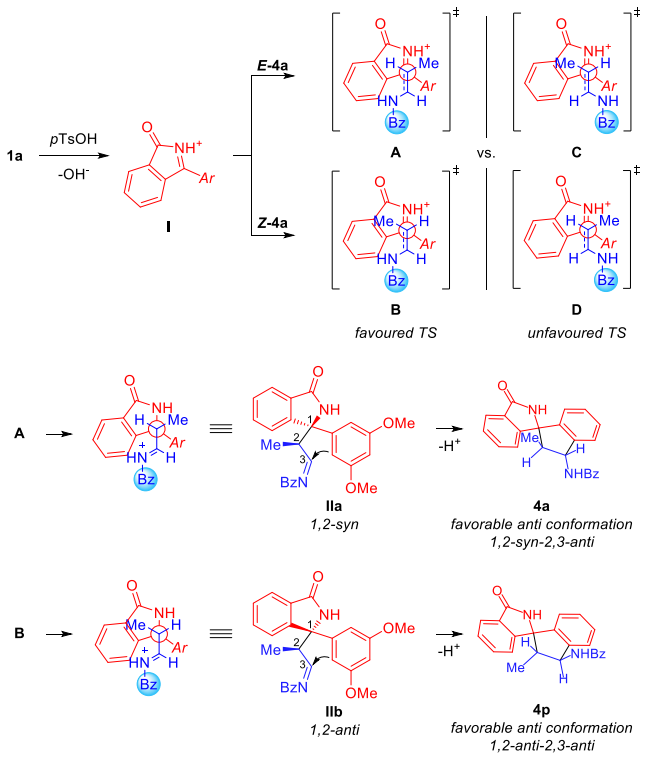


[a]The given yield refers to the isolated yield of the shown major diastereomer (*dr* >98:2:0:0). The reported diastereomeric ratio (*dr*) refers to the diastereomeric ratio of the crude reaction mixture as determined by ^{1}H NMR. Structure of **4p** in the solid state (methyl and aromatic H atoms are omitted for clarity).

Based on the obtained stereoselectivities and the observed reactivity patterns, we assume, our transformation proceeds via a stepwise mechanism (Scheme 3). In the presence of the acid catalyst, a reactive acylimine species **I** is generated from the 3-hydroxyisoindolinone. Addition of the enamide **2a** to the acylimine via an open transitions state affords the 1,2-*syn*-intermediate **IIa** in the reaction with *E*-enamide and the 1,2-*anti*-intermediate **IIb** in the reaction with *Z*-enamide.[14] For the (*E*)-enamide transition state A is favored over transition state B, most probably due to steric repulsion between the amide residue and the bulky aryl group. In a similar manner, the addition of the (*Z*)-enamide proceeds preferably trough transition state C. These newly formed acylimine species (**IIa** or **IIb**) can undergo an intramolecular aza-Friedel-Crafts-type reaction with an electron-rich arene moiety, leading to final spirocyclic product. Apparently, the stereochemical outcome of this intramolecular reaction is solely controlled by the substituent at the C2, leading to the 2,3-*trans*-configured spirocycles **4a** or **4p** with

very high diastereoseletivties in both cases.[15] In the absence of an electron-rich arene moiety, no subsequent intramolecular aza-Friedel-Crafts-reaction can take place. Presumably slow decomposition of the acylimine intermediate **II** takes occurs in these cases (see Scheme 3).

Scheme 3: Proposed, stepwise reaction mechanism.[a]



[a]Bz = benzoyl. Ar = aryl.

In summary, we have reported a novel, Bronsted-acid catalyzed formal [3+2] cycloadditon between enamides and in situ generated acylimine species. This process affords intriguing spiro-fused isoindolinones with three adjacent stereocenters in good to high yields and very high diastereoselectivities. The use of *E*- and *Z*-configured enamides enables a stereoselective access to two different diastereomers of the spirocyclic scaffold. The reaction proceeds via a stepwise reaction mechanism, initiated by an addition of a nucleophilic enamide to an electrophilic acylimine followed by ring-closure via an intramolecular aza-Friedel-Crafts reaction. Studies toward the application of this method for the synthesis of biologically active molecules as well as investigations of an enantioselective version are currently underway in our laboratory.

Experimental Section

For general experimental conditions, detailed experimental procedures, analytical data, and ^{1}H, ^{13}C and ^{19}F NMR spectra, see the Supporting Information. The following procedure serves as a representative example.

GP: Synthesis of Spiroisoindolinones

A flame dried and nitrogen flushed Schlenk tube, equipped with a septum and a magnetic stirrer, was charged with *N*-acylimine precursor **1** (0.50 mmol, 1.0 equiv), enamide **3** (0.625 mmol, 1.25 equiv) and dichloromethane (10 mL/mmol). The reaction was cooled to 0 °C and *para*-toluenesulfonic acid monohydrate (0.05 mmol, 0.1 equiv) was added and the resulting mixture stirred at 0 °C. After TLC analysis of an aliquot showed complete consumption of the *N*-acylimine precursor **1**, the reaction was quenched by addition of saturated aqueous $NaHCO_3$-solution (5 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Purification by flash chromatography (DCM:MeOH = 99.5:0.5 → 19:1) afforded the spiroisoindolinone **4** as analytically pure product.

Supporting Information

Data that refers to the herein described experiments were submitted to the repository chemotion (https://www.chemotion-repository.net/). All DOIs minted for the data are linked in supporting information file 1 and a summary of all new data obtained in this study can be gained with the collection https://dx.doi.org/10.14272/collection/MHA_2023-11-28.[16] The material that was obtained in this study (target compounds, please see supporting information file 2) was submitted to the Molecule Archive at KIT and can be requested from there (https://compound-platform.eu/home).

Acknowledgements

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Keywords: spirocycles • enamide • stereoselective synthesis • spiroisindolinones

References

(1) (a) Cabrele, C.; Reiser, O. *J. Org. Chem.* **2016**, *81*, 10109-10125. (b) Taylor A. P.; Robinson R. P., Fobian Y. M.; Blakemore D. C.; Jones L. H.; Fadeyi O. *Org. Biomol. Chem.* **2016**, *14*, 6611-6637. (c) Taylor R. D.; MacCoss M.; Lawson A. D. G. *J. Med. Chem.* **2014**, *57*, 5845–5859. (d) Reiser O. *Eur. J. Org. Chem.* **2019** *31-32* 4973-4975.

(2) (a) Hiesinger K.; Dar'in D.: Proschak E.; Krasavin, M. *J. Med. Chem.* **2021**, *64*, 150–183. (b) Zheng Y.; Tice C. M.; Singh S. B. *Bioorganic Med. Chem. Lett.* **2014**, *24*, 3673-3682.

(3) (a) Lovering F.; Bikker J., Humblet C. *J. Med. Chem.* **2009**, *52*, 6752–6756. (b) Lovering F. *Med. Chem. Commun.* **2013**, *4*, 515-519.

(4) (a) Wrobel J.; Dietrich A.; Woolson S. A.; Millen J.; McCaleb M.; Harrison M. C.; Hohman T. C.; Sredy J.; Sullivan D. *J. Med. Chem.* **1992**, *35*, 4613–4627. (b) Korch K. M.; Watson D. A. *Org. Lett.* **2021**, *23*, 7285–7289. (c) Sharme S.; Oh Y.; Mishra N. K.; De U.; Jo H.; Sachan R.; Kim H. S.; Jung Y. H.; Kim I. S. *J. Org. Chem.* **2017**, *82*, 3359–3367.

(5) (a) Li, J.; Gu, Z.; Zhao, X.; Qiao, B.; Jiang Z. *Chem. Comm.* **2019**, *55*, 12916–12919. (b) Krishna, Y.; Tanka F. *Org. Lett.* **2021**, *23*, 1874–1879. (c) Yuan W.; Shi B. *Angew. Chem. Int. Ed.* **2021**, *60*, 23187-23192.

(6) (a) Nagamoto M.; Sakamoto K.; Nishimura T. *Adv. Synth. Catal.* **2018**, *360*, 791-795. (b) Nagamoto M.; Yamauchi D.; Nishimura T. *Chem. Commun.* **2016**, *52*, 5876-5879. (c) Nagamoto M.; Nishimura T. *Chem. Commun.* **2014**, *50*, 6274-6277.

(7) Unhale R. A.; Sadhu M. M.; Singh V. K. *Org. Lett.* **2022**, *24*, 3319–3324.

(8) (a) Halli J.; Bolte M.; Bats J.; Manolikakes G. *Org. Lett.* **2017**, *19*, 674–677. (b) Halli, J.; Kramer P.; Grimmer J.; Bolte M.; Manolikakes G. *J. Org. Chem.* **2018**, *83*, 12007–12022. (c) Kramer P.; Manolikakes G. *Synlett* **2020**, *31*, 1027-1032. (d) Krieg S.; Grimmer J.; Kramer P.; Bolte M.; Kelm H.; Manolikakes G. *Angew. Chem. Int. Ed.* **2021**, *60*, 23667-23671. (e) Krieg, S.; Grimmer J.; Pick A. M.; Kelm H.; Breugst M.; Manolikakes G. *Eur. J. Org. Chem.* **2022** *2022*, e202200772.

(9) (a) Kramer P.; Grimmer J.; Bolte M.; Manolikakes G. *Angew. Chem. Int. Ed.* **2019**, *58*, 13056-13059. (b) Halaczkiewicz M.; Kelm H.; Manolikakes G. *Eur. J. Org. Chem.* **2023** *26*, e202201318.

(10) (a) Courant T.; Dagousset G. Masson, G. *Synthesis* **2015**, *47*, 1799–1856. (b) Gopalaiah K.; Kagan H. B. *Chem. Rev.* **2011**, *111*, 4599–4657. (c) Carbery D. R. *Org. Biomol. Chem.*, **2008**, *6*, 3455–3460. (d) Bouchet D.; Varlet T., Masson G. *Acc. Chem. Res.* **2022**, *55*, 3265–3283.

(11) 3-Hydroxyisoindolinones were prepared by the addition of the corresponding organomagnesium or organolithium reagents to phthalimide according to: Unhale R. A.; Sadhu M. M.; Ray S. K.; Biswas R. G.; Singh V. K. *Chem. Commun.* **2018**, *54*, 3516-3519. For further details, see the supporting information.

(12) Enamides were prepared using a Ni-catalyzed isomerization of the corresponding *N*-allylamides according to: Halli J.; Kramer P.; Bechthold M.; Manolikakes G. *Adv. Synth. Catal.* **2015**, *357*, 3321-3324 and Weber F.; Steinlandt P. S.; Ballmann M.; Hilt G. *Synth.* **2017**, *49*, 440-450. For further details, see the supporting information.

(13) Relative configurations of **4a**, **4h** and **4p** were unambiguously assigned by single-crystal X-ray diffraction. Deposition Numbers 2311285-2311287 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service. The relative configurations of all other products were assigned in analogy from the ^{3}J coupling constants and NOE experiments.

(14) The herein observed diaseteroselectivties are consistent with previously reported diaseteroselectivties with acyclic acylimine precursors, see ref. 8 and 9.

(15) During the course of this study, the two remaining diastereomers (1,2-*cis*,2,3-*cis* and 1,2-*trans*,2,3-*cis*) could not be observed, even in the crude reaction mixture.

(16) Hałaczkiewicz, M.; Maraj, A.; Kelm, H.; Manolikakes, G. *Chemotion Repository* **2023**, https://dx.doi.org/10.14272/collection/MHA_2023-11-28