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Influence of *N*-Substitution in 3-Alkyl-3-hydroxyisoindolin-1-ones on the Stereoselectivity of Brønsted Acid-Catalyzed Synthesis of 3-Methyleneisoindolin-1-ones

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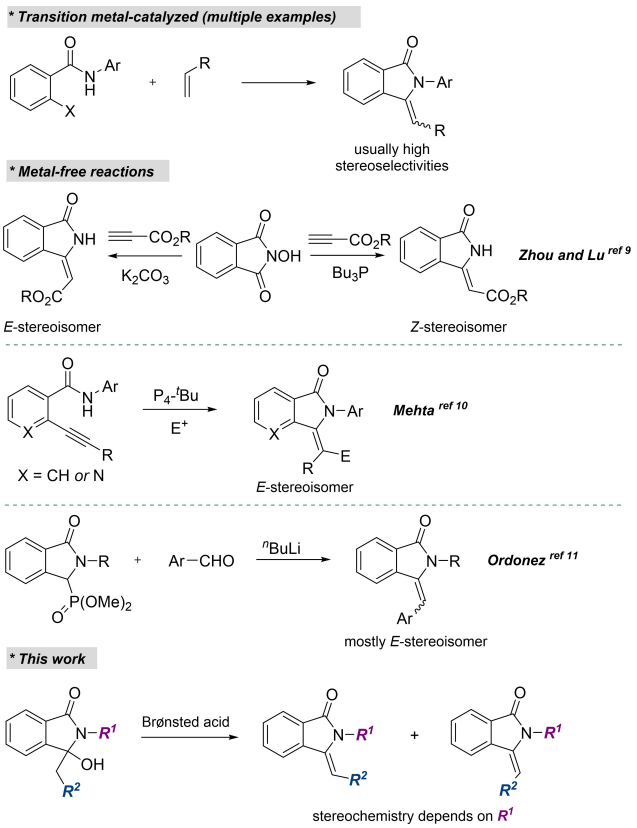
A comprehensive study on the influence of *N*-substitution on the stereoselective outcome of the synthesis of 3-methyleneisoindolin-1-ones from 3-alkyl-3-hydroxyisoindolin-1-ones is reported. The study was performed on an array of structurally diverse 3-alkyl-3-hydroxyisoindolin-1-ones with tunable sizes of *N*-substituents. In a methanesulfonic acid-catalyzed reaction, substrates without *N*-substituent (N–H) afforded exclusively the *Z*-isomer, while an increase in their size was followed by the formation of a stereoisomeric mixture with the *E*-isomer as the major component.

Introduction

Synthesis of 3-methyleneisoindolin-1-ones – ubiquitous compounds found in a broad range of natural products and structurally related pharmaceuticals[1] – has experienced a substantial rise over the years. Consequent advancement in this field has led to numerous creative approaches to these valuable structural motifs (Scheme 1). Strategies utilizing transition-metal complexes are attractive because of their wide functional-group tolerance, effectiveness, and versatility. In this regard, Pd-catalyzed hetero-annulations dominate other accessible methods for the synthesis of these useful heterocycles.[2] In addition, methodologies based on Co,[3] Cu,[4] Ni,[5] Rh,[6] Ru,[7] and Ag[8] catalysis are equally attractive as they provide alternative options for the design of specific synthetic routes comprising 3-methyleneisoindolin-1-ones as intermediates.

Although their metal-free counterparts are not as nearly represented in the literature, several methodologies have emerged in the past decade. Zhou and Lu reported reaction between alkynes and *N*-hydroxyphthalamides where the stereochemical outcome depended on the employed reaction conditions – *E* isomer was preferably obtained in a reaction with potassium carbonate, and *Z* product in a reaction mediated by tributylphosphine.[9] In 2018, Mehta et al developed synthesis of *E*-enamides by a P_4-^{t}Bu catalyzed intramolecular cyclization of 2-alkyne benzamides.[10] By developing the Horner reaction between α-aminophosphonates and aryl aldehydes, Ordóñez et al obtained preferably *E* stereoisomer of the product.[11] Although these are elegant examples for the construction of 3-methyleneisoindolin-1-ones, main drawbacks of majority of the reported methodologies are sometimes tedious prefunctionalizations of starting materials – resulting in the increased step-count, use of expensive reagents and complicated experimental techniques – and regioselectivity issues in cyclization reactions, where the competition between 5-*exo*-dig and 6-*endo*-dig cyclization leads to two structurally different compounds.[14]

The presence of an exocyclic double bond renders 3-methyleneisoindolin-1-ones useful substrates in further functionalization, such as annulation with propargylic alcohols,[12] intramolecular arylation,[13] and oxidative C–H amination.[14] Moreover, several isoindolin-1-one alkaloids exhibiting pain-



Scheme 1. Stereoselective syntheses of isoindolinone-derived enamides.

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alleviating properties contain either *Z*- or *E*-configured stilbenoid unit. Hence, the stereoselective synthesis of such compounds is highly desirable, as it would allow an access to intermediates in syntheses leading to biologically active substances possessing this structural motif with defined C=C double bond stereochemistry that reflects on the chemical behavior.

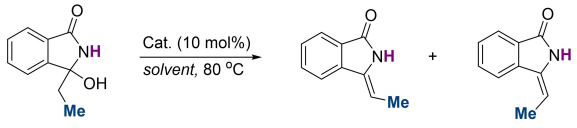
As a part of our ongoing research,[15] we became interested on how the size of the *N*-substituent reflects on the stereochemistry around the exocyclic double bond in the organocatalytic dehydration of 3-alkyl-3-hydroxyisoindolin-1-ones. While addition of organometallic reagents to phthalimide followed by an acidic quench yielding the corresponding 3-methyleneisoindolin-1-ones is already described, to the best of our knowledge, a detailed investigation of the stereochemical outcome of this type of reaction is not reported.

We hypothesized that the formation of the two possible stereoisomers might be mainly affected by the size of the *N*-substituent (Scheme 2). When *N*-substituent is non-existent or small enough, we anticipate preferable formation of *Z* isomer because of the less steric hindrance between the C-3 and *N*-substituents. On the other hand, with a more sterically demanding *N*-substituent, the stereochemical outcome is expected to be inverted; the R group will be steered away from it, affording a *E* stereoisomer as the major product. Easy access to various *N*-aryl 3-alkyl-3-hydroxyisoindolin-1-ones allows tuning the steric effect imposed by the *N*-substituent. Moreover, by allocating the functional groups around the *N*-aryl substituent, the extent of the proposed effect can be tested as well.

Results and Discussion

As there is a lack of information on the catalytic dehydration of 3-alkyl-3-hydroxyisoindolin-1-ones,[16] at the outset, an extensive screening of reaction conditions with respect to type of catalyst, catalyst loading, temperature, and solvent was performed (Table 1). We started our investigations by employing 3-ethyl-3-hydroxyisoindolin-1-one **1a** as a model substrate. Initially, the reaction conditions included acetic acid as a catalyst in acetonitrile at 80 °C. The corresponding product methyleneisoindolin-1-one *Z*-**2a** (*Z*/*E* > 20:1) was afforded in 86% yield after 48 hours (entry 1). The reaction catalyzed with trifluoroacetic acid proceeded in a similar fashion, yielding the product in just slightly better isolated yield, but in substantially shorter time (92%, 2 hours, entry 2). The reaction with *p*-toluenesulfonic acid afforded **2a** in 86% yield within 1 hour (entry 3), while even faster reaction kinetics were observed when the catalytic amount of methanesulfonic acid (MsOH) was employed, yielding the product after merely 15 minutes (entry 4).

Table 1. Screening of reaction conditions.[a]



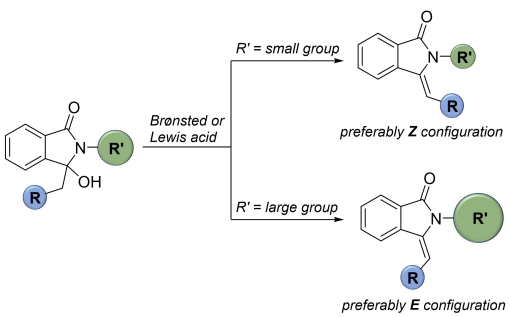
1a → *Z*-**2a** + *E*-**2a**

Entry	Cat.	Solvent	Time [h]	*Z*-**2a**[%]	*E*-**2a**[%]
1	AcOH	acetonitrile	48	86	–
2	TFA	acetonitrile	2	92	–
3	*p*-TsOH	acetonitrile	1	86	–
4	MsOH	acetonitrile	0.25	91	–
5	$PhCO_2H$	acetonitrile	168	88	–
6	DPP[b]	acetonitrile	20	36	–
7	PPA[c]	acetonitrile	20	82	–
8	BF_3xOEt_2	acetonitrile	24	86	–
9	$SnCl_2x2H_2O$	acetonitrile	24	92	–
10	$Pd(OAC)_2$	acetonitrile	24	91	–
11	$ZnCl_2$	acetonitrile	90	81	–
12	$FeCl_3$	acetonitrile	90	70	–
13	$AlCl_3$	acetonitrile	90	81	–
14	MsOH	acetonitrile	24	95[d]	–
15	MsOH	toluene	1	81	–
16	MsOH	cyclohexane	1	89	–
17	MsOH	dichloroethane	1	58	–
18	MsOH	acetonitrile	1	89[e]	–
19	MsOH	acetonitrile	1.5	91[f]	–

[a] Reactions were carried out on a 0.2 mmol scale. Stereochemistry around double bond determined by NOESY experiments. [b] Diphenyl phosphate. [c] Phenyl phosphinic acid. [d] 25 °C. [e] MsOH (5 mol%). [f] MsOH (1 mol%).

On the other hand, benzoic acid, diphenyl phosphate, and phenyl phosphinic acid were inferior compared to MsOH, both in reaction time, and in efficiency (entries 5–7). Since Lewis acids, such as $BF_3 \times Et_2O$, $Ca(NTf)_2$, $Cu(OTf)_2$, and $Sc(NTf_2)_4$, are also capable of initiating dehydration of 3-hydroxyisoindolin-1-ones,[17] we screened several representatives of this type of activators as well. The reaction with $BF_3 \times Et_2O$ under the same reaction conditions resulted in **2a** in 86% isolated yield after 24 hours (entry 8). A similar trend was observed in dehydration catalyzed by $SnCl_2$ and $Pd(OAc)_2$, which resulted in the formation of **2a** in almost identical yield (entries 9 and 10). Other Lewis acids, $ZnCl_2$, $FeCl_3$, and $AlCl_3$ were equally effective, but in all three cases the reaction was completed after 96 hours (entries 11–13).

After identifying MsOH as the best catalyst for the transformation (with respect to yield and reaction time), we turned our attention to investigating the influence of temperature, solvent and catalyst loading. By performing the reaction at 25 °C, the full conversion of the starting 3-ethyl-3-hydroxyisoindolin-1-one **1a** was observed after 24 hours (entry 14). Reac-



Scheme 2. Possible stereoisomers formed in an acid catalyzed dehydration of 3-alkyl-3-hydroxyisoindolin-1-ones.

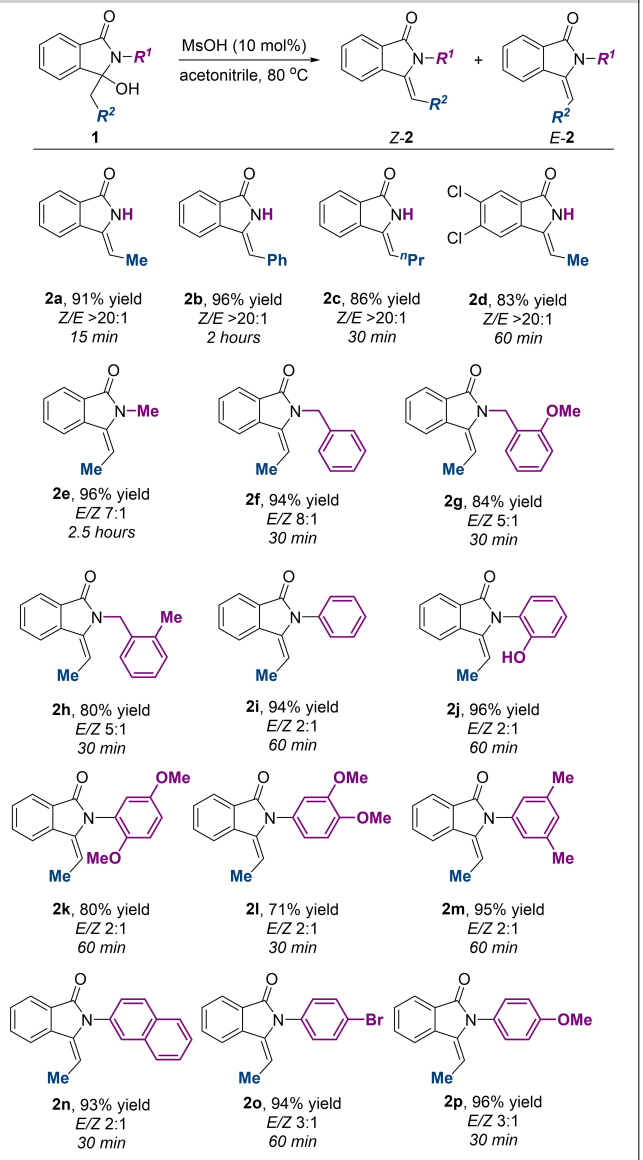
tions in toluene and cyclohexane proceeded smoothly affording the enamide *Z*-**2a** in 81% and 89% isolated yield after 1 hour, respectively (entries 15 and 16). On the other hand, the reaction was not that effective when it was performed in dichloroethane (58%, 1 hour, entry 17). Finally, decreasing the catalyst loading to 5 mol% and 1 mol%, respectively, did not have a significant impact on the reaction outcome with respect to effectiveness, but the reaction time was again longer in comparison to the reaction catalyzed with 10 mol% of MsOH (entries 18 and 19). These results represent useful input for cost effectiveness analysis if the reaction would be run on an industrial scale. Within the frame of screened conditions, the best results were obtained in the reaction catalyzed by MsOH (10 mol%) in acetonitrile at 80 °C.

Next, we turned our attention to investigate substrate scope and limitations (Table 2). Same as the reaction with **1a**, reactions with **1b** and **1c** bearing 3-benzyl and 3-butyl substituents afforded *Z*-**2b** and *Z*-**2c**, respectively, while the formation of the opposite stereoisomers was not detected. Also, dehydration of **1d** proceeded smoothly, affording only *Z*-**2d**, thus indicating that the size of the 3-alkyl substituent does not impose impact on the stereochemical outcome of the reaction. The reaction of **1e** comprising of the *N*-methyl moiety afforded an inseparable mixture of two stereoisomers, *E*-**2e** and *Z*-**2e**, in a 7:1 ratio with a combined isolated yield of 96%. The *N*-benzyl substitution in **1f** had almost the same effect on the stereochemical outcome, where a stereoisomeric mixture was afforded with *E*-**2f** as the major component (*E*/*Z* 8:1). Interestingly, reactions with **1g** and **1h** bearing more sterically demanding MeO and Me groups afforded **2g** and **2h**, both as mixture of stereoisomers in *E*/*Z* ratio 5:1. Contrary to expectations, ratio was even lower comparing to ratio of products obtained in reaction with unsubstituted benzyl group in **1f**. A similar trend was also observed in the reaction with *N*-phenyl substituted starting alcohol **1i**, but in this case a ratio between *E*-**2i** and *Z*-**2i** dropped to 2:1. Dehydration of **1j**, possessing an *ortho*-substituted *N*-phenyl ring, resulted in a mixture of *E*-**2j** and *Z*-**2j** (ratio 2:1) in 96% combined isolated yield. Although a stronger influence of the steric hindrance imposed by the hydroxyl group was anticipated, the isomeric ratio did not change compared to the unsubstituted *N*-phenyl ring. Complementary, the stereoisomeric ratio did not change in dehydrations of **1k**, **1l**, and **1m**, bearing *meta* substituted phenyl ring, and in all cases the formation *E* isomer was predominant.

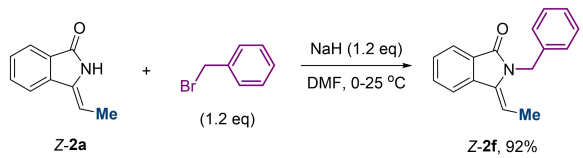
Two stereoisomers were also obtained in the reaction with alcohol **1n** possessing *N*-naphthyl group, again in 2:1 ratio. The presence of *para*-Br and *para*-OMe substituents in **1o** and **1p**, again did not enforce any significant effect on the double bond stereochemistry. In these cases, a mixture of the corresponding enamides was formed in a 3:1 ratio.

Obtained results provide a spring-board for further modification and implementation of the formed enamides into synthesis of compounds with higher molecular complexity and defined stereochemistry. Therefore, we were interested in whether it would be possible to obtain only one stereoisomer simply by changing the order of the synthetic steps. Since the reaction of **1a** yielded product **2a** exclusively as the *Z* isomer, and the reaction of **1f** provided a mixture of two stereoisomers with predominant formation of the *E*-**2f**, we investigated whether *Z*-**2f** could be prepared by a simple *N*-alkylation of *Z*-**2a**. Indeed, the reaction between *Z*-**2a** and benzyl bromide mediated by sodium hydride provided targeted product *Z*-**2f** in 92% isolated yield (Scheme 3).

Table 2. Substrate scope.[a]



[a] Reactions were carried out on a 0.2 mmol scale. *E*/*Z* ratio determined by ^{1}H NMR.



Scheme 3. Approach to the stereoisomer *Z*-**2f**.

This result represents high potential of the developed method, where a set of consecutive steps can lead to a variety of *N*-substituted 3-methyleneisoindolin-1-ones in terms of the stereochemical outcome.

It is well established that the activation of the hydroxyl group in 3-aryl 3-hydroxyisoindolin-1-ones is followed by elimination of a water molecule via rearrangement of an electron pair on the adjacent nitrogen atom, leading to the formation of highly reactive and electrophilic *N*-acyl ketimine.[15d,18] On the other hand, 3-alkyl substituted acyliminum intermediates could isomerize to the corresponding enamides, which hampers the formation of the desired product.[19] Thus, we investigated the competitiveness between the formation of enamide and the addition of an external nucleophile. The reaction between **1a** and indole under standard reaction conditions provided exclusively product **3**, while the corresponding enamide *Z*-**2a** was not detected (Scheme 4). Likewise, Brønsted acid catalyzed aza-Friedel-Crafts arylation of *Z*-**2a** with indole provided product **3** in 85% isolated yield. In a similar fashion, intramolecular cyclization of tryptamine-containing isoindolin-1-one **1q** afforded fused polycycle **4** in 68% isolated yield.

Since it was previously reported that *N*-substitution has a detrimental effect on the rate of ketimine formation[15e] and taking into account differences in reaction times between the *N*-substituted and N–H 3-alkyl-3-hydroxyisoindolin-1-ones, it is reasonable to assume that ketimine forms during the course of the reaction. Dehydration of **1a** occurred within 15 minutes, while in other cases it took up to 2.5 hours for the reaction to complete. Moreover, synthesis of **3** directly from alcohol **1a** was faster compared to its synthesis from enamide **2a** (1 hour vs 24 hours). This observation excludes the possibility of enamide formation and its subsequent conversion to **3** under the used reaction conditions.

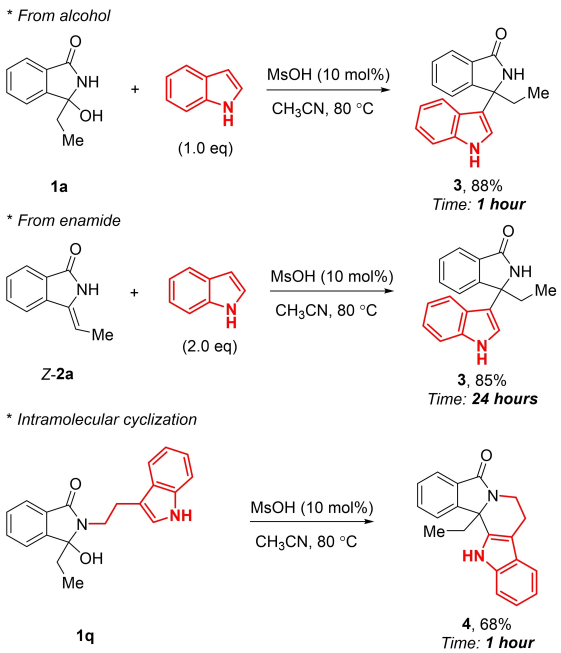
Based on obtained results, we propose the following reaction mechanism (Scheme 5). Protonation of 3-hydroxyisoindolin-1-one **1** affords activated intermediate **II**. Then, water molecule is eliminated to generate a reactive ketimine intermediate **III**. The resulting cation **III** undergoes elimination in two possible ways. If there is no substituent on nitrogen, R^1 group moves away from isoindolinone aromatic ring, and the elimination in **IIIa** results in *Z* product. On the other hand, larger substituents on nitrogen directs R^1 away from it, and β-hydrogen elimination in **IIIb** leads to *E* product.

Conclusion

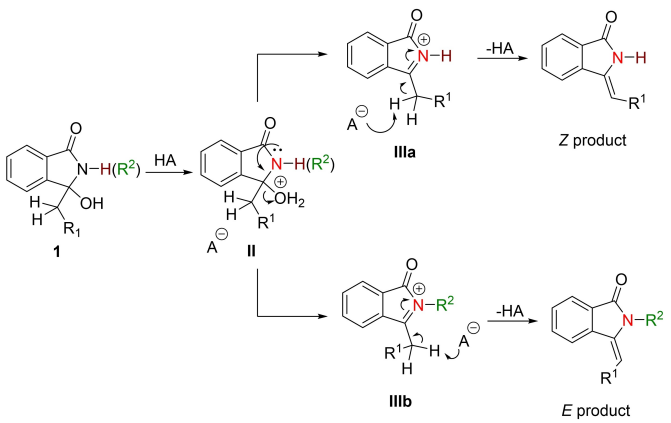
In conclusion, we have demonstrated that the stereochemistry around the C=C double bond in 3-methyleneisoindolin-1-ones, prepared by acid-catalyzed dehydration of the parent 3-alkyl-3-hydroxyisoindolin-1-ones, is affected by the size of the *N*-substituent. A variable steric hindrance imposed by the size of the *N*-substituent is in direct correlation with the stereochemical outcome. With a large group, a stereoisomeric mixture is afforded with the *E*-isomer as the major component. On the other hand, the absence of *N*-substituent leads to an exclusive formation of the *Z*-isomer. Our results provide a background on which the levels of stereoselectivity in these types of reactions can be predicted. Finally, we have also demonstrated that the undesired stereochemistry in 3-methyleneisoindolin-1-ones could be circumvented by changing the order of the synthetic steps.

Experimental Section

General procedure for enamide synthesis. To a suspension of selected 3-alkyl-3-hydroxyisoindolin-1-one[15a] (0.20 mmol) in MeCN (1.0 mL) was added MsOH (0.02 mmol) at 25 °C. Reaction mixture was stirred at 80 °C until the full consumption of the starting material was confirmed by TLC. Pure enamide was obtained by flash column chromatography of the reaction mixture on silica gel.



Scheme 4. Control experiments.



Scheme 5. Proposed reaction mechanism for the formation of enamides **2**.

(*Z*)-5,6-Dichloro-3-ethylideneisoindolin-1-one (*Z*-**2l**). To a suspension of 5,6-dichloro-3-ethyl-3-hydroxyisoindolin-1-one (0.049 g, 0.20 mmol) in MeCN (1.0 mL) was added MsOH (0.0013 mL, 0.02 mmol) at 25 °C. Reaction mixture was stirred for 1 hour at 80 °C. Full consumption of the starting material was confirmed by TLC. Flash column chromatography of the reaction mixture on silica gel (petroleum ether/ethyl acetate 1 : 1, $R_f = 0.57$) afforded 0.038 g (84 %) of the title compound as a greyish solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.25 (s, 1H), 7.88 (s, 1H), 5.92 (q, $J = 7.8$ Hz, 1H), 1.93 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.7, 137.1, 134.9, 132.7, 131.2, 129.4, 124.3, 122.5, 105.7, 12.6; IR (neat) 3058, 2359, 1713, 1285, 987, 770, 630 cm^{-1}; HRMS (MALDI TOF) m/z: $[M+H]^+$ calcd. for $C_{10}H_7Cl_2NO$ 227.9983; found 227.9993.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Catalysis · Enamides · *N*-Substitution · Stereoselectivity · Steric hindrance

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