Asymmetric [4+2] Annulation Reactions Catalyzed by a Robust, Immobilized Isothiourea

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ABSTRACT: A polystyrene-supported isothiourea (**1a**) behaves as a highly efficient organocatalyst in a variety of formal [4+2] cycloaddition reactions. The catalytic system has proven to be highly versatile, leading to six-membered heterocycles and spiroheterocycles bearing an oxindole moiety in high yields and excellent enantioselectivities (32 examples, including the novel oxindole spiropyranopyrazolones **8**). The remarkable chemical stability of **1a** under operation conditions results in high recyclability (11 cycles, accumulated TON of 76.8) and allows the implementation of an extended-operation continuous flow process (no decrease in yield or ee after 18 h).

KEYWORDS. Isothioureas • Enantioselective Catalysis • Solid-Supported Catalysts • Spirocyclic Compounds • Oxindoles

1. INTRODUCTION

Since their introduction by Birman and Okamoto in the last decade,[1] chiral isothioureas have become an important class of enantioselective organocatalysts.[2] As chiral Lewis base catalysts, isothioureas have been explored in a large variety of asymmetric transformations, including acyl transfer,[3] silyl transfer,[4] formal pericyclic[5] and domino reactions.[6] Considering the importance of this type of catalyst in organic synthesis and our continuing interest toward the immobilization of homogeneous catalytic species,[7] we recently synthesized a polystyrene-supported isothiourea organocatalyst that was successfully applied in the Michael addition/cyclization reaction with tosylimine derivatives.[8] However, applications of this new immobilized isothiourea catalyst in new transformations have not been investigated in depth. Herein, we report the first enantioselective formal [4+2] cycloaddition reactions between several types of unsaturated heterocycles and *in situ* activated arylacetic acids in a process catalyzed by an immobilized isothiourea catalyst that can be operated in batch and flow.

Heterocyclic compounds containing nitrogen-nitrogen and nitrogen-sulfur arrays are frequently encountered as privileged structural frameworks in numerous bioactive natural products and pharmaceuticals.[9] Indeed, the pyrazolone, thiazolone or spiro-oxindole pyrazolone scaffolds can be found in antiplatelet,[10] anti-inflammatory,[11] anticancer,[12] kinase-inhibitor[13] and antibacterial[14] compounds (Figure 1). In particular, chiral spirocyclic pyrazolones bearing a quaternary stereocenter (promising subsets of the spirocyclic family) are very interesting, albeit hardly available from a synthetic perspective.[15] Indeed, despite some synthetic efforts devoted to the synthesis of functionalized pyranopyrazolone derivatives,[16] the development of an efficient methodology for the catalytic asymmetric construction of pyranothiazolones[17] and spiro-pyranopyrazolones bearing a quaternary stereocenter is still a challenging endeavor.

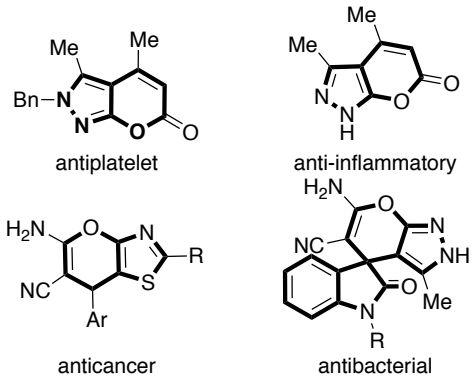
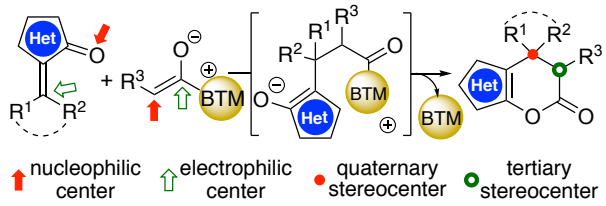


Figure 1. Examples of Biologically Active Pyrazolone and Thiazolone Derivatives.

The exploitation of chiral isothioureas in asymmetric transformations via asymmetric ammonium enolate addition is a well-developed and powerful synthetic strategy.[18] Romo *et al.* have pioneered the *in situ* generation of ammonium enolates from carboxylic acids and their application to a range of aldol-lactonization reactions.[19] Building upon this work, Smith *et al.* have recently utilized chiral isothioureas to promote the intra- and intermolecular asymmetric functionalization of carboxylic acids through a Michael-lactonization cascade reaction,[20] which has also been described with NHC catalysts.[16d, 17, 21] However, the use of isothioureas to promote an asymmetric Michael-lactonization sequence where a quaternary stereocenter is created remains underexplored due to the low reactivity of most substrates. Given the manifold interest of heterocycles of these classes, we wish to report a highly enantioselective version of the ammonium enolate addition involving unsaturated heterocycles and thus leading to a variety of optically pure, functionalized six-membered heterocycles bearing a tertiary or quaternary stereocenter (Scheme 1).

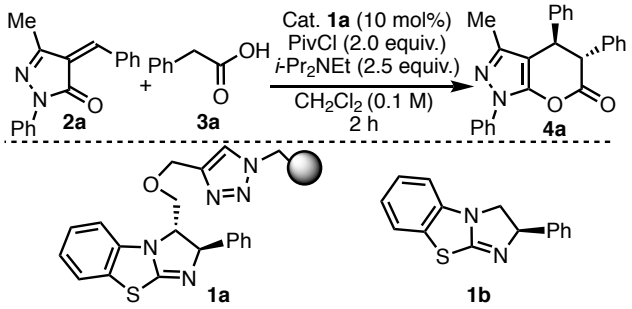
Scheme 1. Formal [4+2] Cycloaddition with Unsaturated Heterocycles.



2. RESULTS AND DISCUSSION

We initiated our study by investigating the reaction of alkylidene pyrazolone **2a** with phenylacetic acid **3a**, using pivaloyl chloride as a reagent to activate *in situ* the carboxylic acid (Table 1). Inspired by previous works, a protocol based on immobilized isothiourea **1a**, PivCl, and *i*-Pr_2NEt in CH_2Cl_2 at room temperature led to full conversion and provided the desired product in good diastereoselectivity and excellent enantioselectivity (entry 1). In contrast, when homogeneous benzotetramisole (BTM, **1b**) was employed, only moderate diastereoselectivity was observed, albeit conversion and enantioselectivity remained the same (entry 2). This points out to an intimate interplay of steric effects that takes place due to the additional stereocenter present in **1a** (the *handle* for immobilization).

Table 1. Optimization of Reaction Conditions.[a]



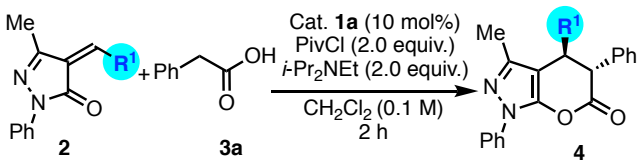
Entry	Modification of std. conditions	Conv. (%)[b]	dr[b]	ee (%)[c]
1	Standard conditions	> 95	8:1	98
2	Using **1b** as the catalyst	> 95	3:1	98
3	Using Et_3N as the base	> 95	5:1	98
4	Using PhCOCl instead of PivCl	55	5:1	98
5	With TsCl instead of PivCl	76	7:1	98
6	With THF instead of CH_2Cl_2	90	3:1	98
7	With toluene instead of CH_2Cl_2	60	6:1	96
8	**Using 2.0 equiv. *i*-Pr_2NEt**	**> 95**	**9:1**	**99**
9	Using 5 mol% catalyst	81	5:1	98

[a] Reactions performed on a 0.1 mmol scale (see Supporting Information). [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC.

Evaluation of the effect of the base employed showed that Et_3N led to lower diastereoselectivity (entry 3). Changing the activating reagent for PhCOCl and TsCl (entries 4 and 5) did not improve the results. Subsequently, solvent screening showed negative impacts on either reactivity or selectivity (entries 6 and 7). We next studied the effect of the relative amounts of the different reactants (see the SI for details) and found that reducing the amount of *i*-Pr_2NEt to 2.0 equivalents afforded the best result in terms of diastereo- and enantioselectivity (entry 8). On the other hand, decreasing the catalyst loading to 5 mol% resulted in lower stereoselectivity (entry 9).

With the reaction conditions optimized for **2a**, we investigated the substrate scope for this asymmetric cycloaddition reaction. As shown in Table 2, the course of the reaction was insensitive to electronic changes at the *meta* and *para* positions of the aromatic substituent R^1 on alkylidenepyrazolones. Specifically, substrates with these substitution patterns (**2b-2g)** underwent reaction in good yields (71-84%), high diastereoselectivities (5:1 to 9:1 dr) and excellent enantioselectivities (97-99% ee), both for electron-withdrawing or electron-donating *m*- or *p*- substituents. The *ortho*-substituted derivative **2h** required longer reaction times (6 h), but gave the desired product **4h** in excellent diastereoselectivity (>20:1 dr), comparable enantioselectivity (99% ee) and good yield (68%). Furthermore, **4i** bearing a heteroaromatic 2-thienyl group was also formed in good yield, excellent diastereoselectivity, and comparable ee (96%). On the other hand, the use of alkyl-substituted acetic acids failed to give good levels of conversion (see Supporting Information for unsuccessful substrates).

Table 2. Scope of the [4+2] Cycloaddition: Alkylidene Pyrazolones.[a]

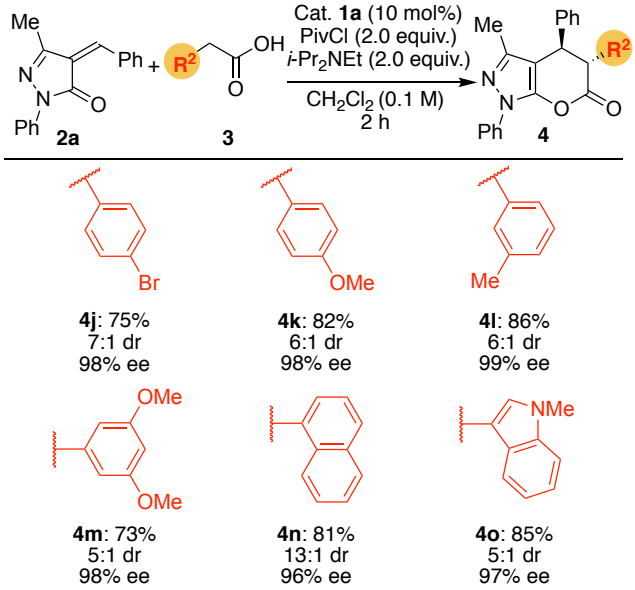


Entry	R^1 (**2**)	Yield (%) (**4**)[b]	dr[c]	ee (%)[d]
1	Ph (**2a**)	83 (**4a**)	9:1	99
2	4-Br-C_6H_4 (**2b**)	83 (**4b**)	9:1	99
3	4-Cl-C_6H_4 (**2c**)	81 (**4c**)	7:1	98
4	4-F-C_6H_4 (**2d**)	82 (**4d**)	8:1	98
5	4-Me-C_6H_4 (**2e**)	72 (**4e**)	5:1	99
6	3-Cl-C_6H_4 (**2f**)	84 (**4f**)	7:1	97
7	3-Me-C_6H_4 (**2g**)	71 (**4g**)	7:1	99
8	2-MeO-C_6H_4 (**2h**)	68 (**4h**)[e]	>20:1	99
9	2-thienyl (**2i**)	81 (**4i**)	6:1	96

[a] Reactions performed on a 0.1 mmol scale (see Supporting Information). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral HPLC. [e] Reaction time: 6 h.

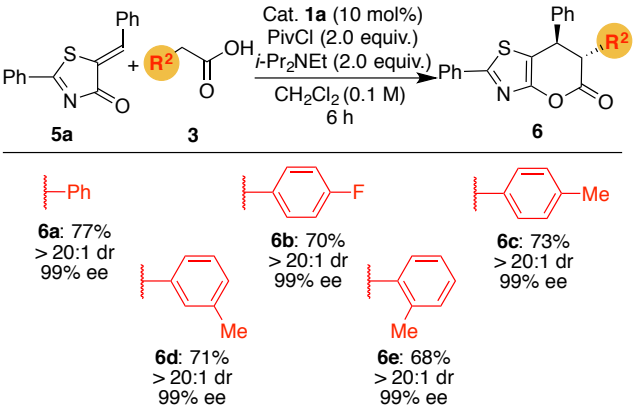
Next, the [4+2] cycloaddition with a variety of arylacetic acids was investigated under the optimized conditions (Scheme 2). A range of arylacetic acids with diverse electronic and steric properties worked well, giving rise to cycloadducts **4j-4n** in good yields (73-86%), excellent ee's (96-99%) and good diastereoselectivities (5:1-13:1 dr). Acid **3o**, bearing an *N*-methylindole substituent, showed no decrease in yield or stereoselectivity.

Scheme 2. Scope of the [4+2] Cycloaddition: Arylacetic Acids.



Dihydropyranothiazolones are another class of nitrogen-sulfur heterocycles present in several drug candidates. This encouraged us to study their ability to be engaged as substrates in an analogous transformation. Gratifyingly, cycloadducts **6** could be accessed under similar reaction conditions. Following a brief screening of reaction conditions, the reaction of alkylidenethiazolone **5a** with substituted arylacetic acids furnished dihydropyranothiazolones (**6a-6e**, Scheme 3) in excellent enantio- (99%) and diastereoselectivities (>20:1 dr), with yields ranging 68–77%.

Scheme 3 Scope of Substituted Arylacetic Acids with a 5-Alkylidene Thiazolone.



With the aim of probing the versatility of this strategy, we prepared different disubstituted alkylidenepyrazolones, which would afford the corresponding cycloadducts bearing an all-carbon quaternary stereocenter (see Scheme 4 and SI). While most disubstituted alkylidenepyrazolones did not engage in the reaction, the isopropylidene derivative afforded the desired product **8a** in poor yield but excellent enantioselectivity (96% ee). Based on this observation, we wondered whether an isatin derivative of the pyrazolone, would undergo the annulation reaction thanks to the less sterically demanding nature of the substrate. This would give rise to functionalized dihydropyranopyrazolones bearing a spirocyclic quaternary stereocenter. With this in mind, we first synthesized an *N*-methyl isatin-derived pyrazolone and performed the cascade [4+2] reaction at 0 ºC. To our delight, the corresponding spiropyranopyrazolone **8b** was obtained in 88% yield with excellent enantioselectivity in a very short reaction time (30 min). The minor, *anti* diastereoisomer was also isolated with high ee values. It is worth mentioning that, to the best of our knowledge, this is the first synthesis of optically pure spirocyclic oxindole-pyranopyrazolone scaffolds.[22] Biological studies to assess the therapeutic potential of these unique structures are currently underway.

Subsequent studies showed the generality of this approach to assemble a range of optically active substituted spiropyranopyrazolones under the established optimal reaction conditions. As indicated in Scheme 4, variations in the electronic properties of the substituents on the benzene ring of the arylacetic acid **3** were investigated and the corresponding spirocyclic adducts (**8b-8g**) were isolated in good yields (81-91%) with high ee's and moderate diastereoselectivities. To emphasize the generality of our approach, various *N*-substituted isatin-derived pyrazolones were also tested and participated equally well in the reaction (**8h-8j**). Furthermore, the extension of the substrate range to electron-poor or electron-rich substituted *N*-methyl isatin-derived pyrazolones was well tolerated, providing the [4+2] annulation products in good yields and excellent ee's (**8k-8l**).

The absolute configuration given for all of the dihydropyranopyrazolones **4**, dihydropyranothiazolones **6** and spiropyranopyrazolones **8** is based on the X-ray analysis of the major diastereoisomers **4b**, **6a**, **8c** and minor diastereoisomer **8c´** (see Figure 2 and SI).

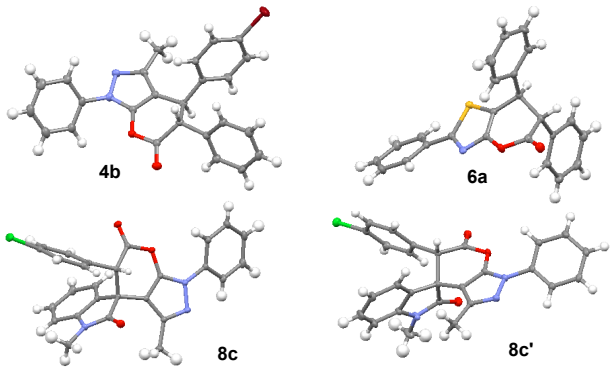
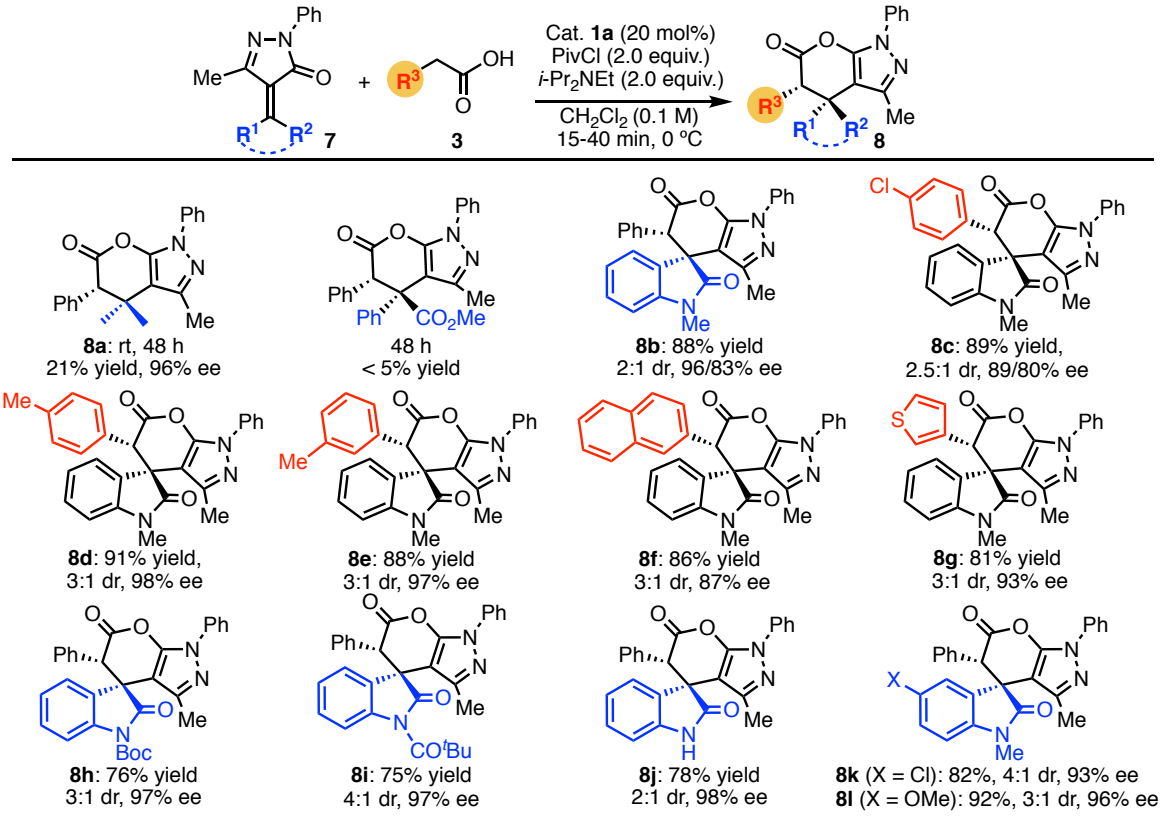


Figure 2. X-ray structures; **4b**: CCDC 1519361; **6a**: CCDC 1519360; **8c**: CCDC 1519359; **8c'**: CCDC 1519358.

From a practical perspective, the use of an immobilized isothiourea catalyst offers the inherent advantages of easy recovery and reuse. Under the standard conditions, we explored the recyclability of catalyst **1a** in the reaction of alkylidene pyrazolone **2a** with phenylacetic acid **3a** as model substrates. After each run, the catalyst could be recovered by simple filtration and reused in the next cycle by adding fresh

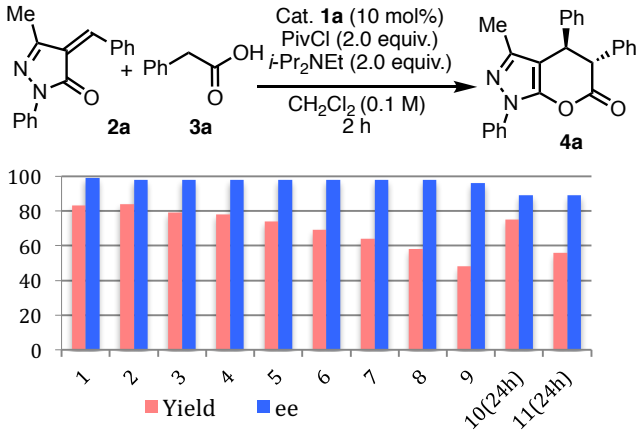
Scheme 4. Scope of the Reaction Between Different Disubstituted Alkylidene Pyrazolones and Arylacetic Acids.



reactants. Keeping the reaction time constant, nine consecutive reaction cycles were performed with 10 mol% of resin **1a**, affording the cycloadducts with constant stereoselectivity and only marginal erosion in the yield (Scheme 5). To gain insight into the recyclability profile of **1a**, the same catalyst was used in two more cycles (reaching a total of 11) increasing the reaction time to 24 h. Under these conditions, product **4a** was obtained in higher yields and slightly lower enantioselectivities. The accumulated TON for the whole recycling experiment was 76.8. Indeed, the robustness of this catalytic system was further proven by implementing an 18-h continuous flow experiment that provided 2.74 g of **4a** (67% yield and 99% ee) as a single diastereomer (see section 7 of the SI for details).

The proposed catalytic cycle for these transformations (Scheme 6) proceeds through initial *in situ* formation of the mixed anhydride **A** from the arylacetic acid, followed by formation of the corresponding acyl ammonium species **B**. This is deprotonated by pivalate (the amine is just a shuttle base)[23] to generate an enolate (**C**) which undergoes stereoselective conjugate addition (**D**), followed by lactonization, giving the cycloadduct product **E** and regenerating the immobilized isothiourea. The proposed approaches of dihydropyranopyrazolone **4** and dihydropyranothiazolone **6** are in accordance to previous reports and configurational analysis. Our current working hypothesis involves an epimerization of the stereocenter α to the lactone C=O, a situation that has been observed for related systems[20e] (see Section 9 in the SI for details).

Scheme 5. Recyclability Test.

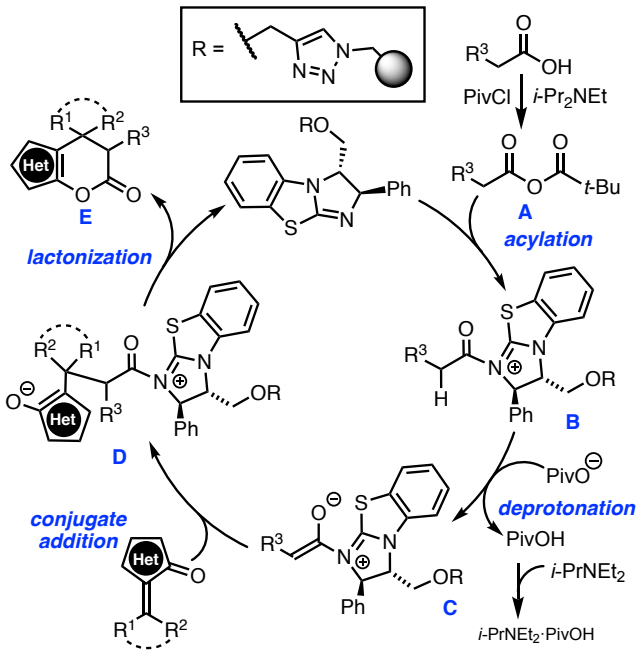


3. CONCLUSIONS

In summary, we have disclosed an asymmetric polystyrene-supported isothiourea catalyzed formal [4+2] cycloaddition of unsaturated heterocycles with *in situ* activated arylacetic acids. The annulation strategy described represents an efficient approach to access a series of dihydropyranopyrazolone and dihydropyranothiazolone derivatives, as well as spiropyranopyrazolones bearing a quaternary stereocenter, in excellent yields and stereoselectivities. Compared to its homogeneous counterpart, **1a** displays higher stereoselectivity and the same reactivity. In addition, it can be recycled at least eleven times by simple filtration of the reaction mixture. Finally, the implementation of a continuous flow process with this catalytic resin illustrates the benefits of this approach. Further appli-

cation of the polystyrene-supported isothiourea catalyst and biological evaluation of the heterocycles prepared is currently underway.

Scheme 6. Proposed Catalytic Pathway.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Electronic Supplementary Information (ESI) available: synthetic procedures, characterization data, copies of NMR spectra and HPLC chromatograms (PDF)

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