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# Identification of New Catalysts to Promote Imidazolide Couplings and Optimisation of Reaction Conditions Using Kinetic Modelling

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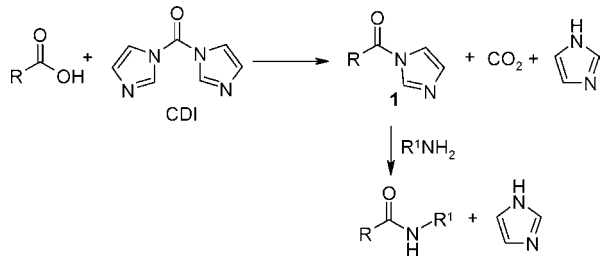
**Abstract:**

**Three catalysts were used to promote an imidazolide coupling. These catalysts were 2-hydroxypyridine (HOPy), *endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximide (HONB) (both reported for the first time to catalyse this type of reaction), and 1-hydroxybenzotriazole (HOBt). The thermal safety, cost, and catalytic effectiveness of these three catalysts are compared. In addition, kinetic modelling using the Dynochem software was used to optimise the HOBt- and HOPy-catalysed reactions. By use of this simulation method, the optimal reaction conditions, such as catalyst quantity, reaction time, and reaction temperature were predicted. Subsequent experiments confirmed that the predictions were accurate.**

## Introduction

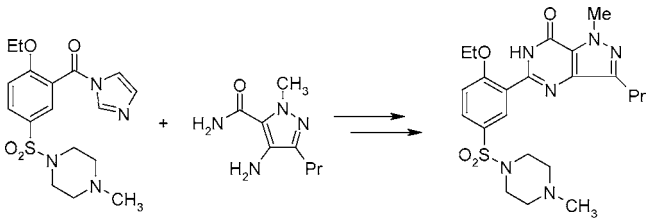
The use of *N*,*N*′-carbonyldiimidazole (CDI) in amide-coupling reactions has been known for nearly 50 years.[1,2] The advantages are that the byproducts, carbon dioxide and imidazole, are innocuous and the evolution of carbon dioxide in forming the imidazolide **1** provides a driving force for the reaction[1,2] (Scheme 1). In addition, the imidazole byproduct can be removed by an acidic wash[3] or can remain in solution in the organic solvent.[4]

***Scheme 1***



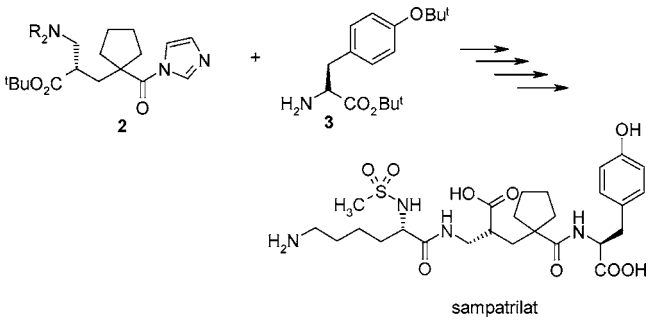

In more recent years, CDI has been used for the large-scale synthesis of a number of pharmaceutical products, e.g. sildenafil[4] (Scheme 2) and sampatrilat[3] (Scheme 3). Both can be prepared from imidazolides, which are made from the corresponding acid and CDI. One factor influencing the increased use of CDI on a large scale is its relatively low price (around $8/mol for a large-scale purchase). Although CDI is more expensive than traditional amide-forming reagents such as thionyl chloride and isobutyl chloroformate, in some cases the high yields and clean environmental conditions can justify its use.

***Scheme 2***




One disadvantage of CDI is that the resulting imidazolide **1** is less reactive than the corresponding acid chloride, and hence amide couplings with either hindered carboxylic acids or weakly nucleophilic amines can be unacceptably slow. One way around this issue is to use 1-hydroxybenzotriazole (HOBt) as a catalyst so that, for example, the hindered imidazolide **2** does not undergo reaction with the tyrosine derivative **3** even in refluxing toluene. As a result, after the addition of 0.1 mol of HOBt the reaction proceeds in 2 h at 95 °C in excellent yield.[4] The additional use of HOBt does, however, have some drawbacks. The material is known to explode when heated beyond its melting point (around 156

***Scheme 3***

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(1) Anderson, G. W.; Paul, R. *J. Am. Chem. Soc.* **1958**, *80*, 4423.
(2) Anderson, G. W.; Paul, R. *J. Am. Chem. Soc.* **1960**, *82*, 4596.
(3) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood A. S. *Org. Process Res. Dev.* **2002**, *6*, 244.
(4) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.


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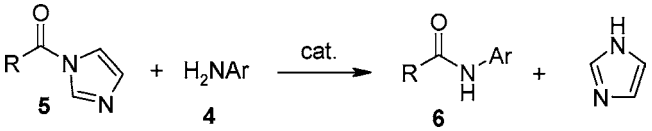
**Scheme 4**




°C).[5] The transportation of HOBt on a large scale is subject to restrictions in Europe because of this explosion potential. It should also be noted that carbon dioxide has also been reported to accelerate imidazolide couplings.[6]

The objectives of the research described in this paper were three-fold: (1) to identify catalysts safer than HOBt, those that retain the ability to promote sluggish imidazolide couplings, (2) to provide, for the first time, quantitative data on the rate of acceleration for three different catalysts, and (3) to demonstrate the use of kinetic modelling to optimise reactions for scale-up.

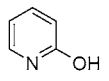
## Results and Discussion

In a reaction studied at Pfizer, it was found that the coupling of an aromatic amine **4** with an imidazolide **5** (Scheme 4) was unacceptably slow, giving around 45% conversion, after 12 h at 78 °C in refluxing ethyl acetate.

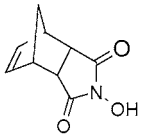
**1. Identification of Safer Catalysts.** The reaction without catalyst was investigated by extending the reaction time, increasing the pressure, using a different solvent with a higher boiling point, and using microwave equipment (Figure 1). Although the conversion with microwave radiation is very encouraging after just 3 h, the scale-up equipment is not widely available.

It was therefore decided to explore the use of a catalyst in the formation of the amide, to maintain the supply of the programme. As mentioned earlier, HOBt has some safety drawbacks having a large energy of decomposition (−1715 J/g with an onset temperature of 159 °C) (Figure 2) when measured by differential scanning calorimetry (DSC) at a heating rate of 5 °C/min.

Hence, a group of alternative catalysts was screened, and 2-hydroxypyridine (HOPy, **7**) and *endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximide (HONB, **8**) gave the most promising leads.




2-hydroxypyridine **7**




*endo*-*N*-hydroxy-5-norbornene-2,3-dicarboximide **8**

HOPy does not have any of the thermal safety issues associated with HOBt. A DSC trace of HOPy shows no evidence of decomposition (Figure 2). HOPy is also cheaper than HOBt on a molar basis. The other alternative catalyst, HONB, has a higher onset temperature than HOBt and a lower energy of decomposition (−876 J/g) (Figure 2). HONB is also the most expensive of the three catalysts. Therefore,

(5) *Brethericks Handbook of Reactive Chemical Hazards*, 6th ed.; Urben, P. G., Ed.; Butterworth-Heinemann: Boston, 1999: p 746.
(6) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P. *J. Org. Chem.* **2004**, *69*, 2565.

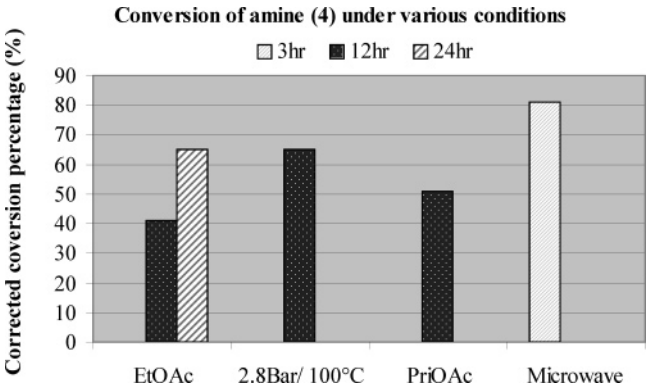



***Figure 1.*** **Solution yield (%) of amide 6 under various uncatalysed conditions.**

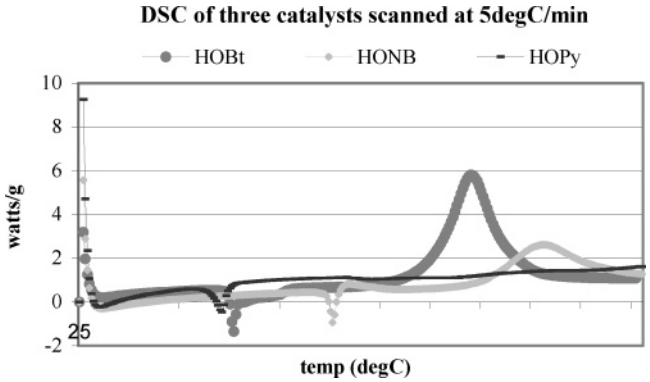



***Figure 2.*** **Differential scanning calorimetry results of HOBt, HOPy, and HONB.**

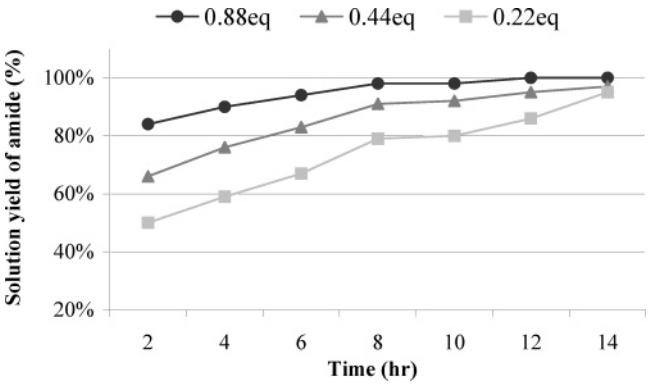



***Figure 3.*** **Solution yield (%) of amide 6 with different levels of catalyst, HOBt, in boiling EtOAc.**

HOPy seemed to be the best catalyst of the three on the grounds of both cost and thermal safety.

**2. Investigation of Acceleration Rate Based on the Quantitative Data.** The HOBt-catalysed reaction was studied at three different concentrations of HOBt, 0.88, 0.44, and 0.22 equiv. The reaction rate was determined from the conversion percentage of amide **6** obtained by HPLC. As seen from Figure 3, there is an acceleration in the rate of reaction with increasing levels of HOBt.

Although process safety screening tests indicated that HOPy and HONB would be safer reagents for scale-up than HOBt, they still needed to give acceptable reaction rates and yields. Like HOBt, HOPy and HONB react

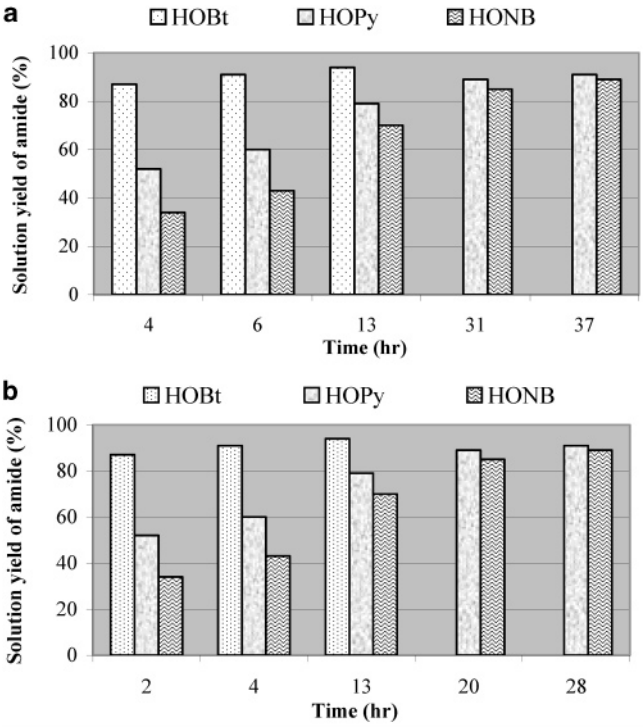



***Figure 4.*** **Solution yield (%) of amide 6 with different levels (0.88 equiv and 0.44 equiv) of catalysts including HOBt, HOPy, and HONB in boiling EtOAc.**

in situ with **5** to give an activated ester, and subsequent reaction with the amine **4** gives the desired amide. The imidazolide **5**, amine **4**, and different levels of catalysts were heated at reflux in ethyl acetate using a Multimax four-vessel reactor system (Mettler-Toledo). The conversion percentages were obtained by HPLC, and the results are given in Figure 4.

From the results in Figure 4, the following conclusions can be made:

- All three additives HOBt, HOPy, and HONB catalyse the reaction.
- The order of the catalytic effectiveness is HOBt > HOPy > HONB.

HOPy is a superior catalyst to HONB in terms of cost, catalytic effectiveness, and thermal safety. Hence, the best two additives for catalysing the reaction of the imidazolide **5** and the amine **4** are HOBt, which is most effective, and HOPy, which is safer and cheaper.

In chemical development, reaction time is not always the rate-limiting factor in a process; in fact, workup, filtration, and drying are often the rate-limiting operations. For this process when the scale and likely cycle time were evaluated, it was decided that ideally the reaction time should be less than 24 h (with a reaction completion target of 95%). Hence, it can be seen that HONB fell far short of these criteria, and work on this catalyst was terminated at this point. From the results in Figure 4, it was clear that HOPy-catalysed reactions would not meet these criteria with a substoichiometric catalyst loading in refluxing ethyl acetate. Hence, to achieve acceptable rates of conversion either more catalyst and/or the use of higher reaction temperatures were needed. However, before any further experimental work was carried out, it was decided to do some kinetic modelling to guide any further experiments.

**3. Demonstration of Kinetic Modelling To Optimise Reactions on Scale-Up.** To the chemist or engineer in academia or discovery chemistry, optimisation of a reaction step often means devising conditions that simply lead to the best yield. To the industrial chemist and engineer involved in research and development, scale-up, and commercial manufacture, optimisation may refer to a combination of factors such as yield, cost, efficiency, or throughput, and several of these experimental responses may have to be optimised concurrently. Dynochem has the capability to help achieve this by building kinetic models from which many reaction possibilities can be simulated.[7]

Given the targets for percentage conversion (95%) and time (24 h) that had been set, the next task was to simulate the optimum catalyst loading for three reactions:

(1) HOBt in boiling ethyl acetate (78 °C),

(2) HOPy in boiling ethyl acetate (78 °C), and

(3) HOPy in boiling *n*-propyl acetate (102 °C).

The three sets of data adapted in Figure 3 were used to build a kinetic model for the HOBt/ethyl acetate reaction.[8] In the model it was assumed that the reaction was third order, i.e.:

$$\text{rate} = k[\mathbf{5}][\mathbf{4}][\text{HOBt}]$$

As the catalyst (HOBt) is regenerated in the reaction, it was assumed that the concentration of HOBt remained constant. Using these assumptions, the modelling package calculates the rate constant as ($k = 3.7 \times 10^{-3}$ dm$^6$ mol$^{-2}$ s$^{-1}$). The kinetic model then allows reactions with any amount of catalyst loading to be simulated.

The two sets of HOPy/ethyl acetate data adapted in Figure 4 were used to build the kinetic model for the HOPy-catalysed reaction in boiling ethyl acetate. Again it was assumed that the reaction was third order, i.e.:

$$\text{rate} = k[\mathbf{5}][\mathbf{4}][\text{HOPy}]$$

and that the concentration of HOPy remained constant. This reaction is obviously slower than the HOBt-catalysed reaction, and hence, the rate constant is smaller ($k = 2.43 \times 10^{-4}$ dm$^6$ mol$^{-2}$ s$^{-1}$).

The results of the simulation for a reaction in boiling ethyl acetate catalysed by 0.88 equiv of HOBt is shown in Figure

(7) Dynochem is a commercially available software package that can aid chemical development by helping to model, simulate, and optimise chemical reactions. One such way this can be done is by fitting a kinetic rate equation to measured reaction rate data such as IR profiles, HPLC data, heat flow ($Q_r$) data, or $T_{reaction} - T_{jacket}$ data. The rate expression for the example reaction: A + B → C. Can take the form shown below: Rate = $k$[A] [B] where $k$ is the rate constant, and [A] and [B] are the concentrations of species A and B, respectively. Dynochem enables the scientist to perform a kinetic fit to the observed data and hence find values of the rate constant, $k$, which fit the rate equation. Once a model is established that fits the actual data, then the model can be used to predict the outcome of previously untried experiments. In this way many scenarios can be examined at the desktop and optimum conditions predicted. If the data do not fit the model, it probably means that the mechanistic assumptions made in formulating the rate equation are incorrect and therefore need to be reexamined.

(8) Although three sets of data were used to build this model, a single set of data (from a single isothermal experiment) could have been used to build this isothermal model.

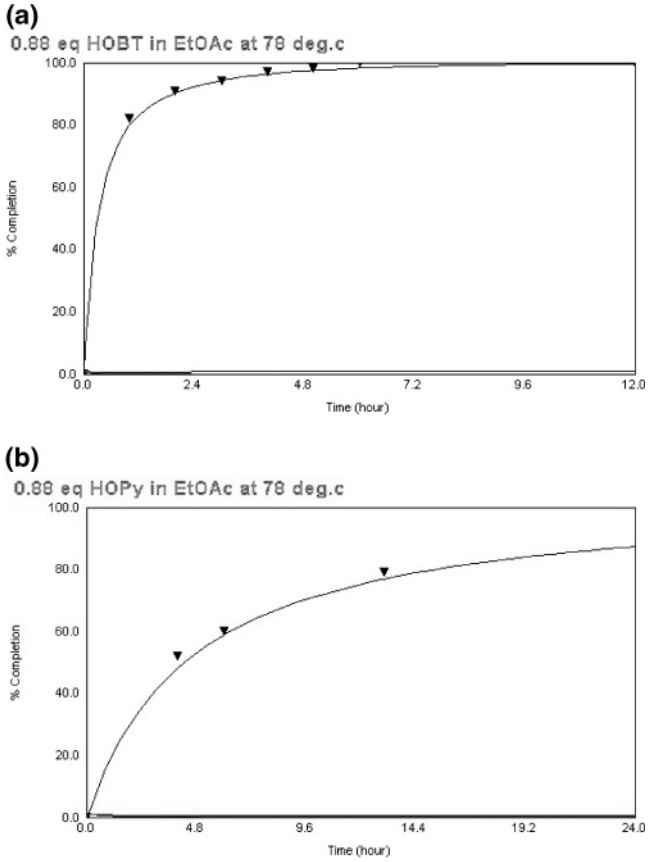



***Figure 5.*** **Kinetic modelling fit and prediction for the formation of amide 6 catalysed by (a) HOBt and (b) HOPy in boiling EtOAc.**

5b along with the results from the actual experiment, and as it can be seen, the "fit" is very good. Although not shown in this paper, the kinetic model also provides an excellent "fit" for the experimental data for the reactions catalysed by 0.22 and 0.44 equiv of HOBt.

The results of the simulation for a reaction in boiling ethyl acetate catalysed by 0.88 equiv of HOPy are shown in Figure 5b along with the results from the actual experiment, and as it can be seen, the "fit" is also good. For the HOPy reaction we also wanted to examine the effect of temperature, and to do this we needed to have an estimate of the energy of activation as shown in the Arrhenius equation given below.

$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

where $k$ is the rate constant, $A$ is the frequency factor, and $E_a$ is the activation energy.

This was done by using a modified form of the above Arrhenius equation which is often more convenient for kinetic fitting as it does not require regression of the rate constants.

$$k = k_{ref} \exp\left(\frac{-E_a}{R}\left[\frac{1}{T} - \frac{1}{T_{ref}}\right]\right)$$

In this expression $k$ is the rate constant at temperature $T$, and $k_{ref}$ is the rate constant at $T_{ref}$. In this method of fitting

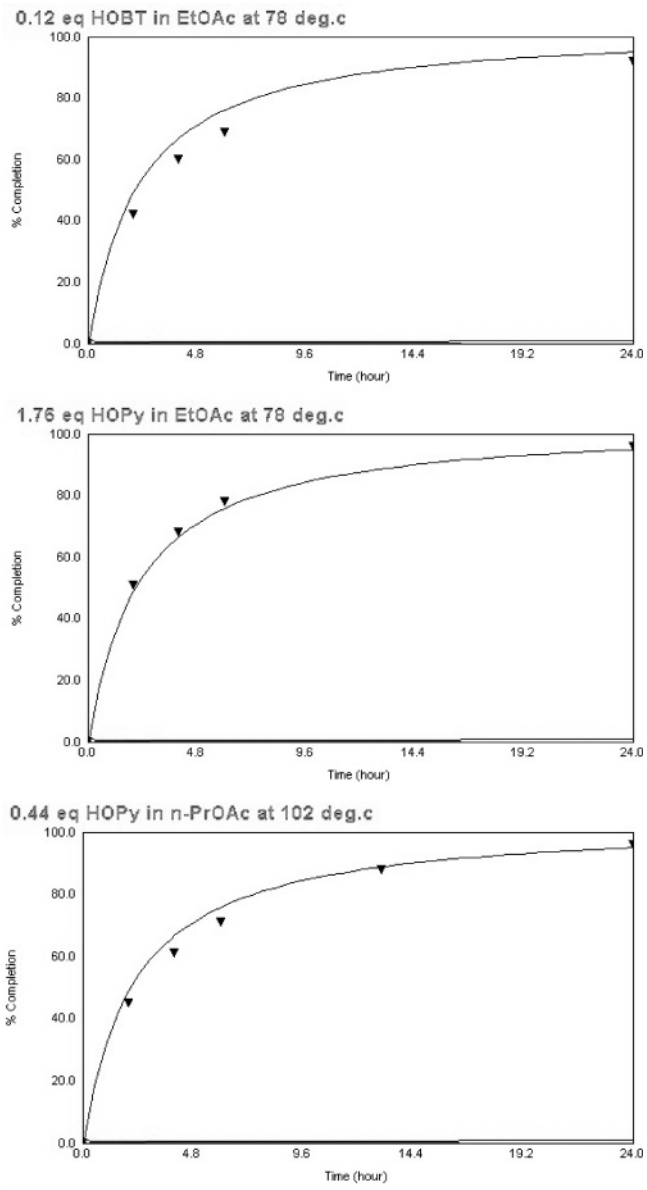



***Figure 6.*** **Kinetic modelling fit and prediction for the formation of amide 6 catalysed by HOBt and HOPy in boiling EtOAc and *n*-PrOAc.**

$k_{ref}$ is held constant, with the Dynochem software calculating (fitting) values of $k$ and $E_a$.

To simulate reactions at different temperature in ethyl acetate and *n*-propyl acetate, a reaction at a different temperature was required to allow estimation of the energy of activation; hence, a reaction was performed with 0.88 equiv of HOPy in boiling *n*-propyl acetate (bp 102 °C).[9] The assumption was made that the kinetics for the reactions in ethyl acetate and *n*-propyl acetate would be similar at the same temperature and concentration. Hence, the *n*-propyl acetate data were entered into the Dynochem software. The rate constant, $k_{ref}$, was set at $6 \times 10^{-4}$ dm$^6$ mol$^{-2}$ s$^{-1}$, and the programme was allowed to estimate the energy of activation by an iterative process. The energy of activation was found to be 49.9 kJ mol$^{-1}$.

(9) The experiment in *n*-propyl acetate gave the following degree of reaction completion at the following time points 2 h (60%), 4 h (74%), 6 h (82%), 13 h (94%), 24 h (98%).

Hence, the kinetic models were now in place, allowing us to simulate and optimise the catalyst loadings. The results are summarised below:

- The optimum level of catalyst for the HOBt/EtOAc reaction was simulated to be 0.12 equiv.
- The optimum level of catalyst for the HOPy/EtOAc reaction was found by simulation to be 1.76 equiv.
- The optimum level of catalyst for the HOPy/*n*-PrOAc reaction was found by simulation to be 0.44 equiv.

These three simulations were then verified by performing the actual experiments, and the results are shown in Figure 6. All three simulations are shown to be highly predictive. Of course if, for some reason, the target conversion and/or the target reaction time changed, i.e. there is a need to increase throughput and reduce reaction time, the new optimised conditions can be simulated from the current models and accurately predicted.

## Experimental Section

**1. Preparation of Imidazolide.** To a vessel dried by boiling with EtOAc was added fresh EtOAc (4 mL/g acid) and 1,1′-carbonyldiimidazole (1.18 equiv) to give a suspension. A freshly made solution of the acid (1.05 equiv) in EtOAc (8 mL/g acid) was added to the suspension over 30 min, and the temperature of this mixture was maintained below 30 °C. This reaction mixture was kept stirring at 20−25 °C until HPLC showed the full conversion of the starting material.

**2. General Procedure for the Formation of the Amide.** Experiments were conducted in a four-vessel Mettler-Toledo multimax system simultaneously on a 50-mL scale. To the imidazolide solution obtained from the previous step was added the desired catalyst (varying amounts) in one portion followed by the addition of a pre-prepared amine solution (1 equiv). The brown suspension was heated to reflux over 1 h and was kept stirring at this temperature for a further 12 h. Some representative samples were taken during this period, and the results were examined by HPLC.

## Conclusions

The promotion of imidazolide couplings by three different catalysts has been studied. HOBt was found to be the most effective catalyst, but HOPy has greater thermal safety, is cheaper (at least on a molar basis), and in the reaction studied, can be made effective by using higher levels of catalyst or higher reaction temperatures.

Microwave technology was identified as an interesting lead to accelerate this type of reaction.

Dynochem kinetic modelling was successfully used to optimise three catalyst/solvent combinations so that each reaction gave a good yield within a reasonable time frame. The Dynochem modelling technique proved to be a very successful optimisation tool, and the application of this technique can hasten data analysis and reagent selection.

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