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Enantioselective Aza-Michael Addition of Imides by Using an Integrated Strategy Involving the Synthesis of a Family of Multifunctional Catalysts, Usage of Multiple Catalysis, and Rational Design of Experiment

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Abstract: A challenging asymmetric reaction (aza-Michael addition of imides to enones) has been optimized through an integrated approach involving the synthesis of a family of organocatalysts, multiple catalysis (usage of additives), and finally with rational exploration of the chemical space by the application of the experiment design.

Keywords: asymmetric catalysis · aza-Michael reaction · enones · imides · synthetic methods

Introduction

Despite the enormous advancements in chiral non-racemic compounds preparation,[1] effective solutions have only been found for a fraction of the known asymmetric transformations. One of the most common approaches pursued to study a new asymmetric reaction with a single catalyst consists in the use of an "enzyme-like" bi- or multifunctional catalyst.[2] In the last few years, another strategy, multiple or cooperative catalysis, also gathered pace. Combinations of non-covalently bound organocatalysts, metal catalysts, biocatalysts, and hybrid systems became increasingly popular to discover new reactivity or to greatly expand the scope of known transformations.[3]

Our aim was to develop a sound integrated methodological approach to optimize "orphan" transformations for which a highly performing catalytic system has not yet been disclosed. In particular, to consider the several variables affecting the outcome of a reaction mediated by using multiple catalysis, a more rational approach with respect to simply trial-and-error was required. To test the validity of our strategy, we did not choose a known simplified model, but rather a specific example lacking an effective solution. Our objective was to mimic the complexity of issues encountered in process chemistry, in which the goal is not to have a transformation with broad scope, but to find the best possible solution for a specific problem.

Results and Discussion

The subject we chose for our study, the addition of imides to enones, is a challenging transformation. Despite the addition reaction of aromatic heterocycles to ketones and aldehydes proceeds in good yield, imides such as succinimide[4a] or the "nitrogen atom synthetic equivalent" non-substituted phthalimide[4b,c] have only been added to unsaturated aldehydes, by means of iminium ion activation.[4d–h] Enones are less prone to form an iminium ion. To extend the addition of imides to the latter compounds is not straightforward and, to the best of our knowledge, this reaction has not yet been reported. The issues to tackle are: 1) Reactivity: imides are weak nucleophiles and simply cyclic enones are not activated enough. 2) Stereoselectivity: the Michael reaction of imides is reversible and the resulting adducts are not configurationally stable. As expected, treating succinimide **1a** with 2-cyclohexen-1-one **2a** no product was isolated, with or without catalyst (quinine **I** or other amines tested, Scheme 1). In contrast, when the especially activated electrophile 2-ethoxycarbonyl 2-cyclohexen-1-one (**2b**)[5] was employed in the reaction catalyzed by quinine **I**, Michael adduct **3a** was obtained, albeit in a low amount. (Scheme 1) To find the best performing catalysts, we screened structures **II–IV** analyzing the crude reaction mixture by HPLC.

Privileged thiourea catalyst **II**, which since its introduction in 2005 has been successfully employed in a vast number of stereoselective reactions,[6] afforded moderate enantioselec-

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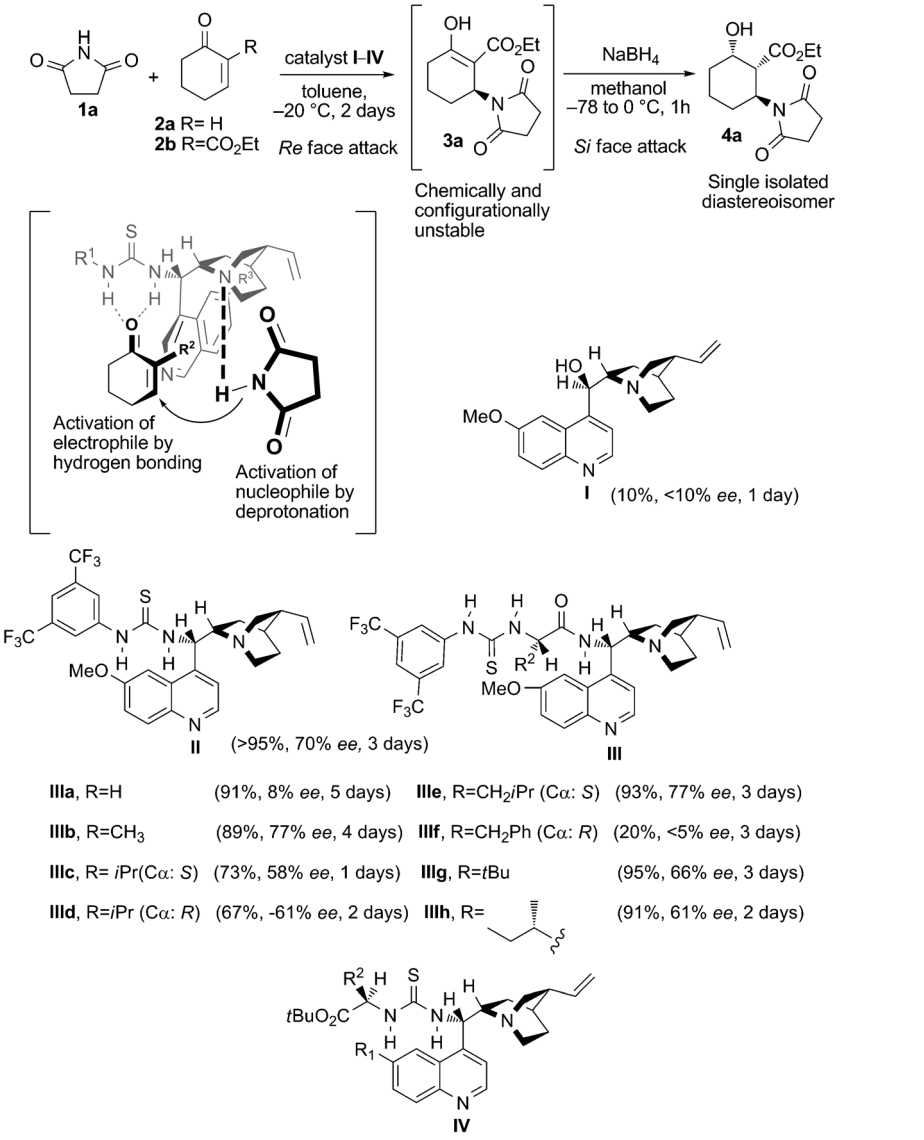


Scheme 1. Screening of catalysts for the asymmetric addition of succinimide **1a** to enones **2a** and **b**. The values in brackets refer to conversion, enantiomeric excess, and reaction time for Michael adduct **3a**. Negative *ee* values indicate the formation of the opposite enantiomer with respect to the one shown. For absolute and relative stereochemical determination of compound **4a**, see the Supporting Information.

tivity [70% enantiomeric excess (*ee*)]. As was anticipated, compound **3a** was both chemically and configurationally unstable, so to determine the yield and reaction enantioselectivity, the reaction mixture obtained employing catalyst **II** was treated with $NaBH_4$ and product **4a** bearing two additional stereocenters, was obtained as single isolated (major) stereoisomer with 70% *ee* and in 62% yield (Table 1, entry 1, and the Supporting Information).[7] A class of several trifunctional amino acid-thiourea catalysts (**IIIa–h**)[8] performing with comparable conversion, gave higher enantioselectivities (up to 77% *ee* employing catalysts **IIIb** or **IIIe**) with respect to catalyst **II**.

We then designed our own family of "tunable" catalysts (**IVa–i**). These structures present the key thiourea moiety flanked by two chiral units. Some of compounds **III** or **IV** lacking the 3,5-bis(trifluoromethyl) group[9] were less active as catalysts with respect to structures such as **II** or **III**. Gratifying, quinine- and cinchonidine-derived catalysts **IVg** and **IVh** afforded the highest enantioselectivity for this specific transformation (Scheme 1 and Table 1, entry 2, 83% *ee* and entry 3, 85% *ee* for compound **4a**). However, the yield of the isolated product after reduction was not optimal.

We then investigated the effect of additives on the reaction enantioselectivity. We found that inorganic Lewis acids (Table 1, entries 4–6) and the organic acid camphorsulfonic acid [(+)-CSA][10] were beneficial in terms of increasing the reaction enantioselectivity. We also tested the reaction with different amount of the additive (+)-CSA, (Table 1, entries 7–11) and found its optimal ratio with respect to catalyst **IVh** (20 mol% catalyst **IVh**, 10 mol% (+)-CSA, Table 1, entry 9). When we attempted to determine the conditions leading to the highest reaction yield we faced a new challenge. Longer reaction times lead to a higher yield of the isolated product, but because of the in situ racemization of intermediate **3a**, longer reaction times were also associated with a lower enantiomeric excess. Chemical transformations in which the enantiomeric excess of the products changes during reaction time are not uncommon, for example, in kinetic resolution. We foresaw that tackling this problem with a rational approach could not only have been beneficial to our specific study, but could serve as a proof-of-

Table 1. Screening of conditions for the one-pot addition of succinimide **1a** to enones **2b** and in situ reduction to afford alcohol **4a** (Scheme 1).

Entry[a]	Cat.	Additive [equiv]	**3a** Conv.[b] [%]	*ee*[b] [%]	**4a** Yield[c] [%]	*ee*[b] [%]
1[d]	**II**	None	>95	70	61	73
2[d]	**IVg**	None	>95	80	59	83
3[d]	**IVh**	None	>95	82	45	85
4	**IVg**	$[Pd(OAc)_2]$ 0.04			26	88
5	**IVh**	$[Pd(OAc)_2]$ 0.04			29	88
6	**IVh**	$NiCl_2$ 0.04			31	85
7	**IVh**	(+)-(CSA) 0.04	93	85		
8	**IVh**	(+)-(CSA) 0.07	90	90		
9	**IVh**	(+)-(CSA) 0.1	74	91		
10	**IVh**	(+)-(CSA) 0.12	70	85		
11	**IVh**	(+)-(CSA) 0.15	<5	rac		
12[e]	none	None	<5	–	–	–

[a] Reaction run employing **2b** (100 mg, 0.595 mmol) and **1a** (1.5 equiv) in toluene (4 mL), with 20 mol% catalysts **IVg** or **IVh** at −20°C. Reaction time: 3 days. [b] Conversion and *ee* value were determined by HPLC. [c] Isolated product yield determined after flash chromatography. [d] Reaction time of 2 days. [e] Reaction time of 12 days. (+)-CSA = camphorsulfonic acid.

concept to develop a standard protocol for scientists dealing with similar issues.

Gaining insight about the mechanism of our target reaction would have been a daunting task. The two diastereotopic transitions states giving rise to the different enantiomers of product **3a** in 90% *ee* differs at RT for less than 2 kcal mol^{-1}. Molecular modeling with DFT calculations would have required input data such as a catalyst with molecular weight of about 600 Da, two non-covalently bound additives, and the effect of the solvent, as well as other parameters. Inevitably, the approximations required to study this model would lead to postulated intermediates that are scarcely reliable. Any insight gained with this approach resulting in a more enantioselective or higher yielding reaction would be most likely obtained thanks to serendipity, rather than a logical strategy. Our target was surely to optimize this reaction, but proceeding through a rational strategy rather than a trial-and-error approach.

For the exploration of the chemical space, we identified some parameters that were most likely influencing the reaction outcome, but whose effect was not clear from the monodimensional screening table routinely reported in the majority of works dealing with asymmetric catalysis. To select the most significant experiments, we employed a computer-assisted set-up of the experiment,[11] which allows a more complete exploration of the multidimensional chemical space. This approach is routinely exploited in process chemistry (DOE or design of experiment), but we are unaware of previous systematic applications screening catalysts or conditions for new asymmetric reaction, like the one described in the present work.[12] The parameters we decided to analyze were: 1) the presence or absence of the additive $[Pd(OAc)_2]$ in addition to (+)-CSA, (discrete variable, which in mathematical terms can assume the values 0 or 1); 2) the choice of the *Cinchona* alkaloid derived catalyst (discrete variable, quinine-based thiourea, **IVg**, value 1, or cinchonidine based-thiourea **IVh**, value 0); 3) the catalyst loading (multilevel variable, with levels 5, 10, and 20 mol%); 3) the reaction concentration (explored by running the reaction at the multilevels 2, 2.5 and 3 mL of solvent: solution concentration: 0.225, 0.178, and 0.148 M, respectively, for 75 mg (0.446 mmol) of substrate **2b**); 4) the reaction time (multilevel variable with levels 2, 3, 5, and 9 days).

The exhaustive exploration of the pentadimensional chemical space would have required $(2\times2\times3\times3\times4)=144$ experiments (full factorial design), with a considerably investment of time and chemicals. The possibility to save on these important resources was of course appealing, but the main feature of this strategy is that the selected experiments are chosen through a rational process rather than in a random way. This approach might even require more time with respect to a trial-and-error approach, but the most significant outcome is that data obtained are much more reliable since they are the result of a logic exploration of reaction conditions rather than "chemical intuition". Thanks to computer-aided experimental design (D-optimal), the rational screening was achieved, thus running the 19 experiments depicted in Table 2.[13a]

We chose response surface methodology (RSM). This explores the relationships between several variables and one or more response variables.[13b] The rationale of RSM is to employ a sequence of designed experiments to obtain an optimal response. Box suggests using a second-degree polynomial model. Despite this model is only an approximation, it is easy to estimate and apply, even when little is known about the process.[13c]

A D-optimal design was then built considering 5 factors (catalyst, addition of $[Pd(OAc)_2]$, catalyst amount, solvent, and time) and the number of experiments to be performed together with set of design points was selected hypothesizing a non-linear effect only for three of the factors (the latter three) and assuming a priori that specific binary interactions could be considered as insignificant.

The best condition led to the isolated product **4a** in 46% yield with 95% *ee* (Table 2 entry 2). We stress the fact that these conditions have been found not by serendipity, but though a systematic exploration of the chemical space. This experimental set-up is an approach to gain insight about our specific problem. To include a statistic treatment of error it would have been necessary to systematically include replicated runs, which would have been beyond the scope of our investigation at this stage.[14,15]

We then tested if the optimal reaction conditions found for the synthesis of compound **4a** would have also been a

Table 2. Design of experiment for the exploratory screening of the asymmetric addition of **1b** to **2a** to afford alcohol **4a**.

Exp.[a]	Catalyst[b]	$[Pd(OAc)_2]$[c]	Catalysts [mol%]	Toluene [mL]	*t* [days]	Yield [%][d]	**4a**, *ee* [%][e]
1	0	1	5	3	9	32	87
2	0	0	20	3	9	46	95
3	1	1	5	2	9	<5	–
4	1	0	20	2	9	33	75
5	0	1	20	2	9	20	85
6	1	1	20	3	9	22	82
7	1	0	5	3	9	11	84
8	0	0	5	2	9	<5	–
9	1	0	10	3	5	14	82
10	0	0	20	2.5	5	22	88
11	0	1	5	2	3	25	86
12	1	0	5	2	2	17	86
13	1	0	20	3	2	25	90
14	1	1	5	3	2	15	84
15	0	0	5	3	2	<5	–
16	1	1	20	2	2	28	85
17	0	1	20	3	2	14	85
18	0	0	10	2.5	2	12	87
19	0	0	20	2	2	27	90

[a] Reaction run employing **2b** (75 mg, 0.446 mmol) and **1a** (1.5 equiv) in toluene, with *x* mol % of catalysts **IVg** or **IVh** (the value of *x* is indicated in column 4) at −20 °C and *x*/2 mol % of (+)-CSA; [b] 0 = cinchonidine-derived **IVh**; 1 = quinine-derived **IVg**; [c] 1 = yes; 0 = no. [d] Yield of the isolated product determined after flash chromatography. [e] The *ee* value determined by HPLC using IA Chiralpack column; see the Supporting Information for all chromatograms.

good starting point for reactions employing similar substrates. Given the different properties of compounds **1**, a separate optimization would have been required for each entry of Table 3.

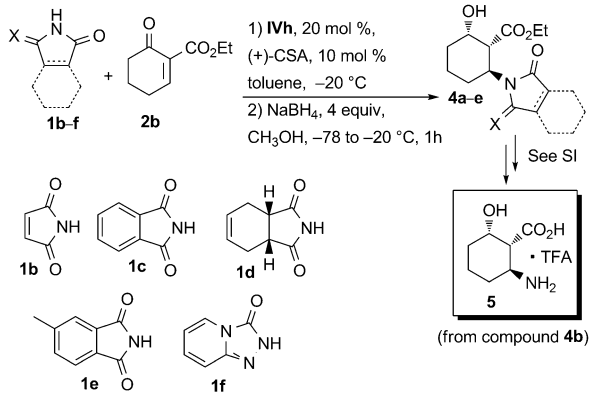
Maleimide **1b** was also a suitable substrate to afford product **4a** (sodium borohydride reduced the double bond moiety to give **4a**, in 41–64% yield, with 90–91% *ee*, entries 1 and 2, Table 3). Imides bearing a cleavable functionality, and therefore more potentially useful as ammonia synthetic equivalent, such as phthalimides **1c–e** afforded the desired adducts (25–56% yield, 75–85% *ee*, Table 3, entries 3–7). The amide and ester functionalities of compound **4b** were cleaved to afford biologically interesting cyclic hydroxy amino acid **5**, see the Supporting Information for details.[16]

It is also worth noting that we were able to introduce imide **1f**, which presents a moiety found in products of pharmaceutical interest such as trazodone.[17] We are unaware if compound **1f** has been employed in any other asymmetric transformation. The reaction afforded compound **4e** in good yield (Table 3, entry 8, 77%); in this case we did not observe the reduction of the amide moiety, which was presumably the main reason why the other compounds **4a–e** were obtained in moderate yields. The reaction enantioselectivity observed for this reaction was high (89% *ee*).

Conclusion

An integrated strategy involving several approaches was pursued to obtain compound **4a** with the highest enantioselectivity possible. Initially, the privileged catalyst **II** afforded **4a** in 70% *ee* (Table 1, entry 1). Then, the family of catalysts **IV** increased this value up to 85% *ee* (catalyst **IVh**, Scheme 1 and Table 1, entry 3). Finally, a rational screening on reaction conditions through a rational set-up of the experiment (Table 2) allowed us to reach 95% *ee* (entry 2). We also confirmed that the results found could be the starting point for the exploration of chemical space with other imides **1b–f**. Was the methodology applied in this work necessary and appropriate, or could the same results have been just achieved by "chemical intuition" and serendipity? We were indeed interested to optimize this specific transformation, but our long term goal was mainly to develop a logic and effective protocol to tackle similar problems for which no acceptable solution currently exists. The conditions we found are not ideal for a scalable process because of long reaction times and moderate yield. However, our findings represent today state-of-the-art to obtain densely functionalized adducts **4**. These conditions have been pinpointed with a rational investigation, rather than a "Eureka" approach. This strategy represents, in our opinion, the most effective and rational way to explore the chemical space in the fast growing field of multiple catalysis, in which several variables should

Table 3. Scope of the reaction of imides **1b–f** with enone **2b**.



Entry[a]	Imide **1**	Yield [%][b]	*t* [days]	d.r.[c]	*ee* [%][c]
1	**1b**	**4a**, 41[d]	3	>20:1	91
2	**1b**	**4a**, 64[d,e]	6	>20:1	90
3	**1c**	**4b**, 36	4	7:1	80
4	**1c**	**4b**, 40[e]	4	7:1	82
5	**1d**	**4c**, 56[e]	7	>20:1	75
6	**1e**	**4d**, 30	5	5:1	82
7	**1e**	**4d**, 25[e]	5	5:1	85
8	**1f**	**4e**, 77	2	>20:1	89

[a] Reaction run employing **2b** (100 mg, 0.595 mmol) and **1b–f** (1.5 equiv) in toluene (0.198 M, 3 mL), with catalysts **IVh** (20 mol%) at −20 °C. [b] Yield of the isolated product determined after flash chromatography. [c] Diastereomeric ratio (d.r. determined by ^{1}H NMR spectroscopy; *ee* value determined by HPLC. [d] The isolated product of this reaction is the fully reduced compound **4a**. [e] Substrate (75 mg, 0.250 M) was employed.

be considered. We hope that our results may benefit other researchers facing similar issues.

Experimental Section

Typical experimental procedure (optimized) for asymmetric synthesis of cyclohexanol 4a: Succinimide **1a** (66 mg, 0.666 mmol, 1.5 equiv), catalysts **IVh–g**, (20 mol%, 0.2 equiv), and (+)-CSA (10 mg, 10 mol%, 0.1 equiv) were placed in a vial with toluene (2.5 mL). The resulting suspension was stirred and cooled at −20°C and then 2-ethoxycarbonyl 2-cyclohexen-1-one **2b** (75 mg, 0.446 mmol, 1.0 equiv) was added dissolved in 0.5 mL of toluene (cooled at −20°C). After 9 days, the reaction mixture was added to MeOH (10 mL) placed at −78°C and $NaBH_4$ (66 mg, 1.786 mmol, 4.0 equiv) was added. The reaction was stirred at −78°C for 30 min , and then warmed up within 30 min at −20°C. Water (2.5 mL) and ammonium chloride (80 mg) were then added. The resulting mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over magnesium sulfate and the filtered solution evaporated in vacuo. The crude material was purified by column chromatography (CH_2Cl_2/ethyl acetate) to afford 55 mg (46% yield) of compound **4a** with 95% *ee* isolated as single stereoisomer.

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see: b) H. Tye, *Drug Discov. Today* **2004**, 485; c) G. E. P. Box, N. R. Draper, *Empirical Model-Building and Response Surfaces*, Wiley, New York, **1986**.

[14] To gain an estimated of this data reproducibility, we replicated in a new experimental set-up the reaction to prepare **4a** with the optimal condition reported in Table 2 (entry 2, 9 day reaction time). Results found in entry 2: compound **4a**: isolated in 46% yield, with 95% *ee*. Replicated run 1; **4a**: 51% yield, 95% *ee*. Replicated run 2; **4a**: 56% yield, 94% *ee*; see the Supporting Information for details.

[15] For an intriguing discussion about chemical intuition and quantitative data treatment in organic synthesis see: R. Carlson, T. Hudlicky, *Helv. Chim. Acta* **2012**, *95*, 2052.

[16] See the Supporting Information for the reaction conditions. Cyclohexyl cyclic amino acids analogous to **5** have been found to exhibit several biological activities, for example, as an anti-hair-graying agent: a) R. Deta, Y. Nakazawa, H. Iwaki, A. Ishino, M. Tajima, World Patent EP1806121(A1), **2007**; as an antidiabetic b) S. D. Larsen, M. A. Connell, M. M. Cudahy, B. R. Evans, P. D. May, M. D. Meglasson, T. J. O'Sullivan, H. J. Schostarez, J. C. Sih, F. C. Stevens, S. P. Tanis, C. M. Tegley, J. A. Tucker, V. A. Vaillancourt, T. J. Vidmar, W. Watt, J. H. Yu, *J. Med. Chem.* **2001**, *44*, 1217–1230, and antifungal agents c) J. Mittendorf, F. Kunisch, M. Matzke, H.-C. Militzer, A. Schmidt, W. Schönfeld, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433–436.

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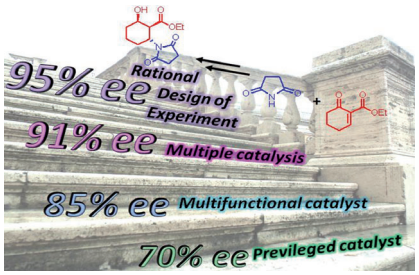
Eureka! versus rational: No "eureka!" moment, but rather a rational step-by-step improvement. The optimization of a challenging reaction was achieved by using an integrated approach involving the synthesis of a family of organocatalysts, multiple catalysis, and through a rational exploration of chemical space with the application of the experiment design in asymmetric catalysis (see figure).



Asymmetric Catalysis

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Enantioselective Aza-Michael Addition of Imides by Using an Integrated Strategy Involving the Synthesis of a Family of Multifunctional Catalysts, Usage of Multiple Catalysis, and Rational Design of Experiment