Tetrahedron Letters 57 (2016) 4599–4603

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Towards a universal organocatalyst for the synthesis of enantioenriched phenylalanine derivatives by enantioselective decarboxylative protonation

Morgane Pigeaux [a], Romain Laporte [a], David C. Harrowven [b], Jérôme Baudoux [a,*], Jacques Rouden [a,*]

[a] Normandie Univ., LCMT, ENSICAEN, UNICAEN, CNRS, 6 Boulevard du Maréchal Juin, 14000, France
[b] Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom

ARTICLE INFO

Article history:
Received 13 July 2016
Revised 24 August 2016
Accepted 1 September 2016
Available online 2 September 2016

Keywords:
Organocatalysis
Decarboxylation
Cinchona alkaloids
Squaramides
Amino acids

ABSTRACT

Access to enantioenriched non-proteogenic phenylalanine derivatives is described using the enantioselective decarboxylative protonation reaction of amidohemimalonate esters catalysed by various cinchona-based compounds. This study compares the catalytic efficiency as well as the enantioselectivity induced by three types of common organocatalysts, namely thioureas, squaramides and bis-cinchona squaramides. One of the main outcome of this work is the observation of a significant influence of the *N*-protecting group of the hemimalonate on its interaction with the catalyst. This methodology carried out under mild conditions exhibits good substrate scope and functional group tolerance. A substoichiometric amount of catalyst can also be used in certain cases while affording good yields and selectivities.

In recent years, considerable effort has been devoted to the preparation of enantiomerically enriched non-proteinogenic α-amino acids. Analogues of phenylalanine have been a particular focus as they are to be found as constituents in many natural peptides and natural products and are a common chiral building block in drug discovery.[1] Although several catalytic reactions have been developed to facilitate their efficient preparation,[2] very few avoid the use of rare and/or hazardous metals.[3] As a consequence, the organocatalytic electrophilic alkylation of glycine enolates under phase-transfer conditions has become established a favoured protocol for the synthesis of many α-amino acids.[4] Though useful, the procedure does have some drawbacks. These include the high cost of starting materials that ensure high enantioselectivity, such as *N*-(diphenylmethylene)-glycine *tert*-butyl ester, and the need to hydrolyse both the imino and ester groups, which can be challenging in the presence of other sensitive functionalities.

Recently, we introduced an alternative organocatalytic strategy for the preparation of α-amino acids based on an enantioselective decarboxylative protonation (EDP) of hemimalonates. We found that such processes were conveniently conducted under phase transfer conditions and could be mediated by hybrid thiourea–cinchona alkaloid catalysts.[5] However, when we came to apply the method in the context of total synthesis, it became clear that our procedure required improvement if it were to become competitive. To that end we decided to set a series of ideals against which an improved organocatalytic protocol might be judged.

These requirements were: (a) the ability to access both enantiomers with good enantioselectivity; (b) mild conditions compatible with reactive functional groups; (c) the use of cheap and commercially available starting materials so that large scale syntheses are practicable; (d) useful timeframes within which the reaction can be realised and (e) a unified catalyst capable of reliably effecting the reaction over a wide range of substrates.

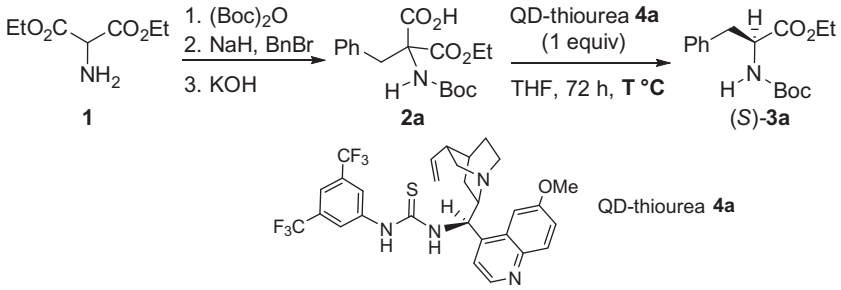
Although our published EDP procedure met many of these criteria, it had some limitations. In particular, its slow rate of conversion was a primary concern as it typically required up to 7 days and a stoichiometric level of catalyst to deliver products in high yield. Moreover, while we were usually able to identify a good catalyst for a given substrate, individual catalysts showed considerable variance when challenged with a range of substrates. Thus, our main goal was to identify a single organocatalyst capable of performing the reaction well at substoichiometric levels over a broad range of substrates within a useful timeframe. Herein we describe our progress to achieving those demanding goals.

Model substrate **2a**, having a Boc *N*-protecting group for ease of removal, was prepared in three steps and 56% overall yield from diethyl aminomalonate **1**. Our first task was to assess its performance in the EDP reaction at various temperatures to identify a

* Corresponding authors.
E-mail addresses: jerome.baudoux@ensicaen.fr (J. Baudoux), Jacques.rouden@ensicaen.fr (J. Rouden).

http://dx.doi.org/10.1016/j.tetlet.2016.09.001
0040-4039/

Table 1
Synthesis of precursor **2a** and temperature dependence of EDP



Entry	Substrate	*T* (°C)	Yield (%)[a]	*er* (%)[b]
1	**2a**	0	20	69:31
2	**2a**	25	40	85:15
3	**2a**	30	68	84:16
4	**2a**	40	94	82:18
5	**2a**	60	95	75:25

[a] Isolated yield. Starting material is the only other compound detected in the reaction for yields lower than 90%.
[b] *er* values were determined by chiral HPLC analysis.

good compromise between reaction time and enantioselectivity for the synthesis of protected phenylalanine **3a**. The reaction time was fixed at 72 h, QD-thiourea **4a** (1 equiv) was employed as the catalyst and THF as solvent, as these conditions regularly gave the best outcomes in our earlier studies.[6] The outcomes from that series of experiments are summarised in Table 1.

Notably, the yield continued to rise as the temperature was increased but enantioselectivity peaked at 25 °C (entry 2), implying that this was the temperature of isoinversion for the EDP reaction.[7] Our discovery of an isoinversion temperature has important implications as these typically arise in reactions where two enantiomers are formed through the same mechanism. Thus, the concentration of the *R* and *S* isomers is proportional to the rate constants for protonation of the two enantiofaces of the enolate, k_R and k_S. The temperature of isoinversion corresponds to the point at which the dominance of enthalpy over entropy switches.

From this study we were able to prepare phenylalanine **3a** with an *er* of 82:18 in 94% yield when the reaction was conducted at 40 °C (entry 4). It should be emphasised that the isolated yields quoted for all of the EDP reactions described in this article reflected the level of conversion, as in all cases starting material and catalyst were the only other compounds found in the product mixtures. Our attention now turned to the influence of the *N*-protecting on the course of the reaction. DFT calculations had indicated that a strong H-bond might form between the carbonyl of *N*-protecting group and the thiourea in the catalyst.[8a] If true, we reasoned that the EDP reaction might perform better with substrates bearing other protecting groups.

To that end a series of hemimalonates with Cbz, Ac, CHO and *o*-$NO_2C_6H_4$ N-protection, **2b**–**2e**, were prepared and tested in the EDP reaction with thiourea catalyst **4a** or its pseudoenantiomer **4b**[8b] (Table 2). For this study the reaction time was fixed at 72 h and temperature was fixed at 30 °C.

The Cbz protected precursor **2b** gave the corresponding amino acid with an *er* of 84/16 but its conversion was slow (entry 3). Indeed, it exhibited the same trends as the Boc protected precursor **2a** in respect of the influence of temperature on selectivity (not shown). Acetate **2c** gave the best enantioselectivity in this series (entry 4).[5a] Faster conversion rates were given by the formyl and *o*-nitrobenzoyl analogues, **2d** and **2e**, but these came at the expense of *er* (entries 5–8). The results support our hypothesis that H-bonding between the carbonyl of *N*-protecting group and the thiourea in the catalyst is a critical interaction.

Our attention next turned to the organocatalysts. In particular, we were drawn to a report by Rawal et al. featuring hybrid squaramide–cinchona alkaloid catalysts.[9a,b] Although studies on such systems were limited,[9c,d] they seemed to function in a manner akin to the thiourea-based catalysts we had been using, making them worthy of study in this context. Moreover, the groups of Song and Soos[10] had each reported that the slow rate of reactivity of thiourea and squaramide organocatalysts was due, at least in part, to self-aggregation and that squaramides bearing two cinchona alkaloid residues often performed better.[10c] Thus, in our search for a universal catalyst for the EDP reaction, we decided to prepare six squaramide–cinchona alkaloid hybrid catalysts, **5a**–**c** and **6a**–**c**, and tested in our model EDP reaction using hemimalonate **2c**. Again, all reactions were conducted at 30 °C in THF for 72 h using the catalysts in stoichiometric and substoichiometric amounts. The results attained are summarised in Table 3.

Compared to thiourea **4a**, the QD-squaramide hybrid catalyst **5a** gave a higher yield but reduced enantioselectivity in favour of the product (*S*)-**3c** (Table 3, entry 1). The related bis-QD-squaramide hybrid **6a** performed similarly in respect of yield but showed a significant improvement in respect of enantioselectivity (Table 3, entry 2). The pseudo-enantiomer **5b** performed worse, affording the (*R*)-**3c** in moderate yield and comparable *er* (entry 3). Notably, the related bis-QN-analogue **6b** performed much better, giving (*R*)-**3c** in 89% yield with an *er* of 80:20 (entry 4). Their performance was in stark contrast to that exhibited by the cinchonidine series (CD), where the bis-alkaloid hybrids performed worse than the mono-alkaloid hybrids (entries 5 and 6).

Buoyed by these encouraging results, we next examined the performance of each catalyst when used at substoichiometric levels. Notably, using 20 mol % of each hybrid in the EDP reaction, bis-QD-squaramide **6a** again emerged as the best organocatalyst in terms of yield and enantioselectivity (Table 3, entry 8). The others, while affording good selectivity in some cases (e.g., **5b**, entry 9; **5c**, entry 11), exhibited very slow conversion rates as evidenced by the poor yields attained for **3c** following work-up. With some promising new catalysts identified, our attention now turned to an assessment of their universality.

To that end, hemimalonates **7**–**9** were each synthesised and their performance assessed in the newly established EDP protocol using QD-thiourea **4a** and bis-QD-squaramide **6a** as organocatalysts. For comparison, the performance of QN-squaramide **5b** was also tested in some cases.