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Organocatalysis

Catalytic Enantioselective Pictet–Spengler Reaction of α-Ketoamides Catalyzed by a Single H-Bond Donor Organocatalyst

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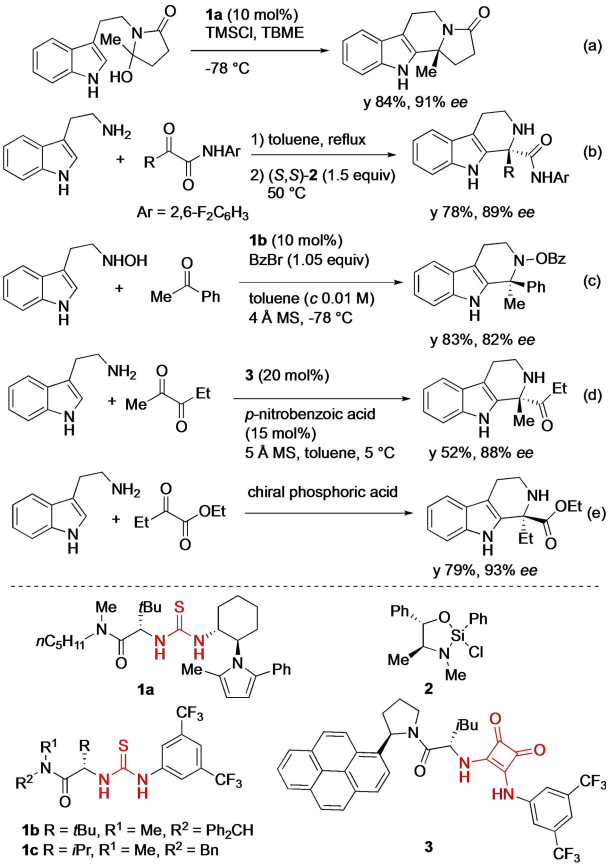
Abstract: The asymmetric Pictet–Spengler reaction (PSR) with aldehydes is well known. However, PSR involving ketones as electrophilic partners is far-less developed. We report herein the first examples of catalytic enantioselective PSR of tryptamines with α-ketoamides. A new class of easily accessible prolyl-urea organocatalysts bearing a single H-bond donor function catalyzes the title reaction to afford 1,1-disubstituted tetrahydro-β-carbolines in excellent yields and enantioselectivities. The kinetic isotope effect using C2-deuterium-labelled tryptamine indicates that the rearomatization of the pentahydro-β-carbolinium ion intermediate might be the rate- and the enantioselectivity-determining step.

Tetrahydro-β-carboline is an important structural motif widely present in bioactive natural products and pharmaceuticals.[1] The Pictet–Spengler reaction (PSR) between tryptamine and carbonyl compounds is arguably one of the most direct and efficient ways to access this important heterocycle.[2] As the reaction generates a stereocenter, the development of the asymmetric PSR has attracted the attention of synthetic chemists for decades.[2] However, it was not until 2004 that Taylor and Jacobsen reported the first chiral thiourea-catalyzed enantioselective PSR of in situ generated *N*-acyliminium salts.[3] Since this pioneering work, other organocatalysts including chiral phosphoric acids (CPA)[4] and squaramides[5] have been developed for the enantioselective PSR of aldimines, as well as cyclic *N*-acylketiminiums with defined C=N double bond geometry (Scheme 1a).[6] Isatines[7] and α-oxo-δ-lactams[3e,4h] have also been successfully engaged in asymmetric PSR.[8,9]

Notwithstanding the aforementioned achievement, the catalytic enantioselective PSR with acyclic ketones remains scarce. The difficulty to control the double-bond geometry of ketimine intermediates and the diminished reactivity of ketimine relative to aldimines could be the reasons that hamper the development of such a transformation. To the best of our knowledge, there are only four examples dealing with the enantioselective PSR with acyclic ketones. Leighton developed the first examples of chiral Lewis acidic chlorosilane (**2**, 1.5 equiv) promoted enantioselective PSR of tryptamines with linear α-ketoamides (Scheme 1b).[10] Snyder and co-workers reported recently a thiourea (**1b**)-catalyzed reaction of *N*-hydroxyl tryptamines with ketones involving a nitrone intermediate (Scheme 1c).[11] In connection with the total synthesis of arborisidine, our group reported a squaramide (**3**)-catalyzed PSR between tryptamine and pentane-2,3-dione (Scheme 1d).[5b] Very recently, Nakamura reported a CPA-catalyzed enantioselective PSR



Scheme 1. Asymmetric Pictet–Spengler reaction (PSR) involving ketiminium intermediates: literature precedents.

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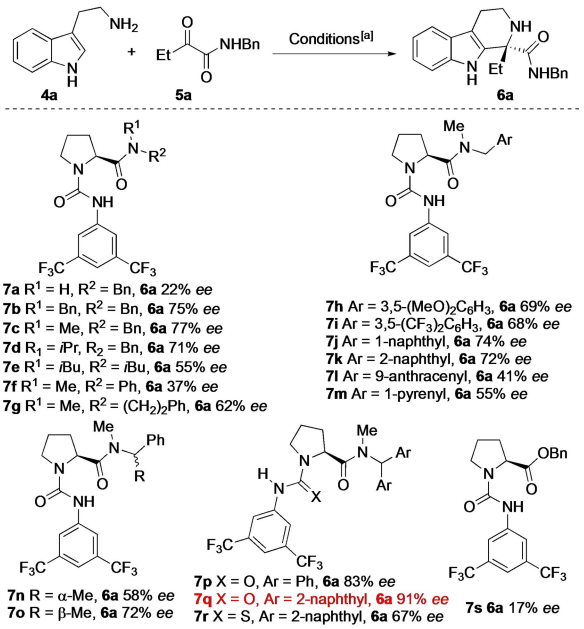
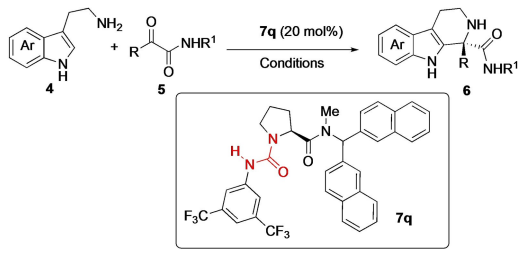
involving α-ketoesters as electrophiles (Scheme 1e).[12] It is important to note that 1,1-disubstituted tetrahydro-β-carbolines have been found in a number of bioactive natural products such as ecteinascidins,[13] peganumine,[14] arborisidine,[15] subincanadine alkaloids[16] and is a much sought-after skeleton in medicinal chemistry.[17] The development of a catalytic enantioselective PSR with ketones is therefore a challenging yet important endeavor.[18] We report herein that a new class of prolyl-urea organocatalyst **7q** bearing a single H-bond donor function is capable of catalyzing the reaction of tryptamines **4** with acyclic α-ketoamides **5** to afford 1,1-disubstituted tetrahydro-*β*-carbolines **6** in high yields and enantioselectivities (Scheme 2). While proline-derived polypeptides have been developed extensively as organocatalysts by the group of Miller,[19] the simple prolinamides of type **7** has, to the best of our knowledge, never been utilized in catalytic asymmetric transformations.

Tryptamine (**4a**) and *N*-benzyl-2-oxobutanamide (**5a**) were chosen as our test substrates. Both thiourea **1c** and squaramide **3** (cf. Scheme 1) were able to catalyze the PSR between **4a** and **5a** leading nevertheless to product **6a** with low *ees* of 23 % and 38 %, respectively (cf. Supporting Information). Inspired by Jacobsen's recent mechanistic studies on the thiourea/benzoic acid-catalyzed PSR,[3d] we hypothesized that the dual H-bonding donor property of the classic (thio)urea catalyst **1** might not be a prerequisite for the enantioselective PSR of α-ketoamides assuming that the rearomatization of the pentahydro-β-carbolinium intermediate is the rate- and the enantioselectivity-determining step. We therefore set out to examine the catalytic activity of the easily accessible simple prolinamide derivatives. Over thirty catalysts derived from (*S*)-proline were evaluated (see Supporting Information for details) and the most relevant results are summarized in Scheme 3. Whereas secondary amide **7a** (R^1 = H, R^2 = Bn) was ineffective, tertiary amides (**7b**–**7d**) catalyzed the reaction to afford **6a** with over 70 % *ee* validating therefore our initial assumption. Increasing amide bulkiness (**7e**) and replacing the benzyl group by a phenyl (**7f**) or a phenethyl group (**7g**) diminished the enantioselectivity of the reaction. Changing the benzyl to 3,5-dimethoxybenzyl (**7h**) or 3,5-di(trifluoromethyl)benzyl (**7i**) groups and switching the phenyl to the extended aromatic rings such as naphthyl (**7j, 7k**), anthracenyl (**7l**) or pyrenyl (**7m**) failed to improve the *ee* of **6a**. Introducing a second stereocenter had little impact in one case (**7o**) and led to diminished enantioselectivity in the mis-matched case (**7n**). Fortuitously, using prolinamides (**7p**, **7q**) derived from *N*-methyl-1,1-diarylmethanamines, **6a** was produced with 83 % and 91 % *ee*, respectively. Interestingly, the thiourea counterpart **7r** catalyzed the reaction with much lower enantioselectivity (67 % *ee*) than **7q**. Finally, the reaction catalyzed by benzyl ester **7s** afforded **6a** in only 17 % *ee*. Fine-tuning the reaction parameters (see Supporting Information) using (*S*)-**7q** as a catalyst allowed us to identify the following optimum conditions: stirring a solution of **4a** and **5a** in a solvent mixture (toluene:hexane = 5/1, *c* 0.04 M) at 110 °C for 10 h followed by addition of catalyst (*S*)-**7q** (20 mol%), *o*-nitrobenzoic acid (15 mol%) and 5 Å molecular sieves (MS) (400 mg/mmol^{-1} of **4a**) at room temperature. Under these conditions, the desired product **6a** was isolated in 94 % yield with 95 % *ee*. It is important to note that a) the presence of MS, preactivated at 200 °C in a vacuum oven, is essential for the reaction. Water adsorption could be the major role of MS since an isolated imine, dried by azeotropic evaporation, underwent the PSR smoothly without MS; b) *o*-nitrobenzoic acid is required to ensure the occurrence of the PSR indicating the weak activating power of the catalyst **7q**.

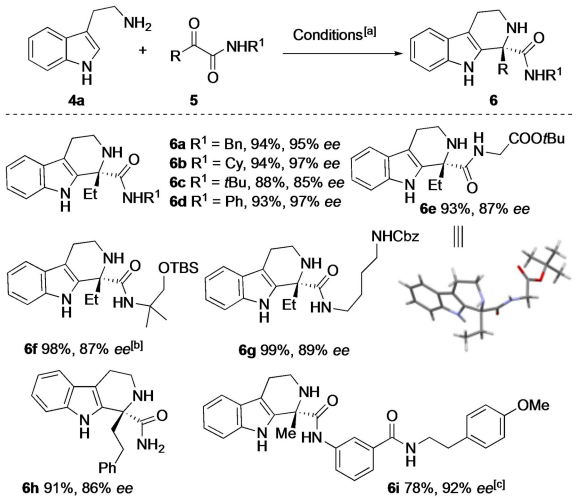
The scope of this prolinamide (*S*)-**7q** catalyzed PSR between tryptamines **4** and α-ketoamides **5**, prepared by amidation of commercially available α-ketoacids or from aldehydes and isocyanides,[20] was next examined (Scheme 4). Since Leighton's conditions worked well only with amides derived from specific anilines (2,6-di$FC_6H_3NH_2$ and 3-$CF_3C_6H_4NH_2$),[10] the amide part of **5** was examined first. As it is depicted in Scheme 4, reaction of **4a** with α-ketoamides derived from benzylamine, cyclohexylamine,



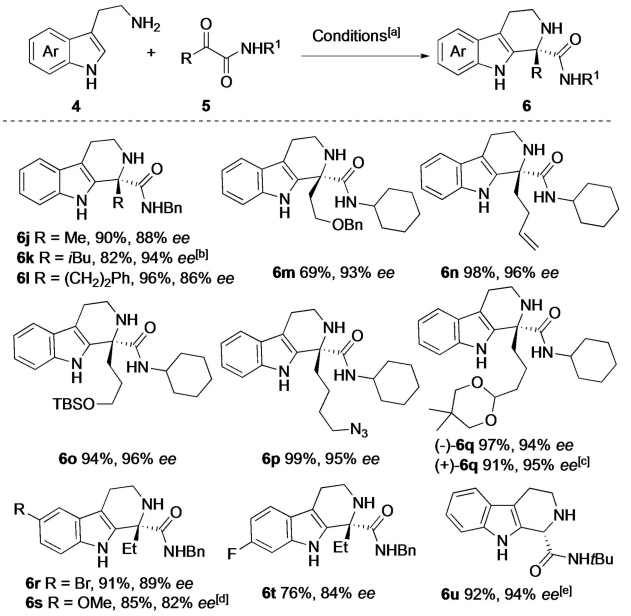
Scheme 3. Catalyst screening. Yields were not determined for these reactions. [a] **4a** (1.0 equiv), **5a** (1.2 equiv), toluene (*c* 0.04 M), 110 °C, 10 h, then catalyst **7** (20 mol%), *p*-nitrobenzoic acid (15 mol%), 5 Å molecular sieves (300 mg/mmol^{-1}), RT.



Scheme 2. Prolinamide-catalyzed enantioselective PSR of tryptamines with acyclic α-ketoamides.



Scheme 4. Scope of (*S*)-**7q**-catalyzed PSR of tryptamine with α-ketoamides: the amide part. [a] **4a** (0.4 mmol), **5** (0.48 mmol), toluene/hexane (v/v = 5/1, *c* 0.04 M), reflux; then (*S*)-**7q** (20 mol%), *o*-nitrobenzoic acid (15 mol%), 5 Å molecular sieves (400 mg/mmol^{-1}), RT. [b] The reaction was performed at 50 °C on gram scale (6.24 mmol of **4a**). [c] The reaction was performed at 0 °C.



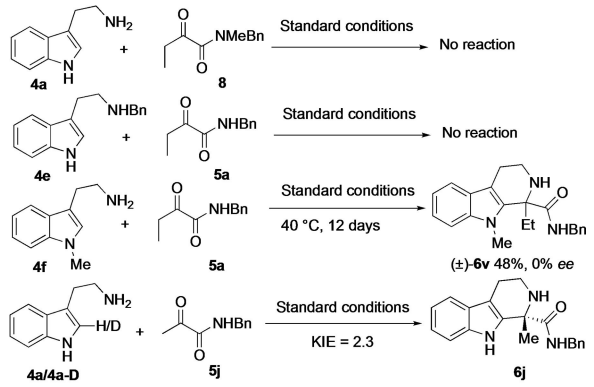
Scheme 5. Scope of (*S*)-**7q**-catalyzed PSR: variation of tryptamine and ketone parts. [a] **4** (0.4 mmol), **5** (0.48 mmol), toluene/hexane (v/v = 5/1, *c* 0.04 M), reflux; then (*S*)-**7q** (20 mol%), *o*-nitrobenzoic acid (15 mol%), 5 Å molecular sieves (400 mg/mmol^{-1}), RT. [b] The reaction was performed at 40 °C. [c] (*R*)-**7q** (20 mol%) was used as a catalyst. [d] The reaction was performed at 0 °C. [e] The reaction was performed at −10 °C.

tert-butylamine and aniline afforded the corresponding 1,1-disubstituted tetrahydro-β-carbolines **6a**–**6d** in uniformly high yields and *ees*. Additional functions in α-ketoamides such as ester (**6e**), silyl ether (**6f**) and carbamate (**6g**) were all tolerated. The presence of an additional secondary amide function did not alter the enantioselectivity as **6i** was isolated in 78 % yield with 92 % *ee*. Primary amide also participated in the reaction to afford **6h** in excellent yield and *ee*. Finally, a gram scale reaction was performed to provide **6f** in 98 % yield with 87 % *ee*. The absolute configuration of **6e** was determined by X-ray crystallographic analysis[21] and the absolute configuration of the other products was assigned accordingly.

α-Ketoamides **5** with diverse range of alkyl residues were next examined (Scheme 5). As expected, enantioenriched tetrahydro-β-carbolines bearing a 1-methyl, 1-ethyl, 1-isobutyl, and 1-phenethyl groups were accessible (**6j**–**6l**, and Scheme 4). Functional groups such as benzyl ether, silyl ether, double bond, azido and ketal functions were all compatible with the reaction conditions (**6m**–**6q**), underlining the mildness of the process. When (*R*)-**7q** was used as a catalyst under otherwise identical conditions, (+)-**6q** was isolated in similar yield and *ee* (91 % yield, 95 % *ee*). 5-Bromotryptamine, 5-methoxytryptamine and 6-fluorotryptamine participated in the reaction with *N*-benzyl-2-oxobutanamide to afford the corresponding adducts without event (**6r**–**6t**), indicating that the presence of both electron-withdrawing (F, Br) and donating groups (OMe) on the aromatic ring were tolerated. Finally, reaction of tryptamine with *N*-(*tert*-butyl)-2-oxoacetamide afforded product **6u**, patented for its immunodeficiency virus inhibitory properties,[22] in 92 % yield with 94 % *ee*. In this later case, preformation of imine has to be avoided and the reaction was performed at −10 °C to ensure high enantioselectivity. A control experiment indicated that **6u** was configurationally stable under the reaction conditions. Finally, the reaction is not without limitation. The reaction of tryptamine with sterically hindered *N*-benzyl-3-methyl-2-oxobutanamide, *N*-benzyl-3,3-dimethyl-2-oxobutanamide and *N*-benzyl-2-oxo-2-phenylacetamide afforded the corresponding products in good yields but with low to moderate *ees* (45 %, 49 %, 13 % *ee*, respectively, see Supporting Information).

A series of control experiments were performed in order to decipher the structural elements needed for the enantioselectivity. No reaction took place when tryptamine (**4a**) and *N*-benzyl-*N*-methyl-2-oxobutanamide (**8**) were submitted to the standard conditions, neither for the reaction between N_b-benzyl tryptamine (**4e**) and **5a** (Scheme 6). The PSR between N_a-methyltryptamine (**4f**) and **5a** occurred only at 40 °C leading to racemic **6v** after extended reaction time (12 days). The results of these control experiments indicated that both the indole N_a-H and the iminium N_b-H of the tryptamine as well as the amide *N*-H of the α-ketoamide are important for both the reactivity and the enantioselectivity of the present PSR. Finally, a KIE of 2.3 was determined (average of three experiments) for the reaction of **4a** and C2-deuterium labelled tryptamine **4a**-D with *N*-benzyl-2-oxopropanamide (**5j**), suggesting that rearomatization of the pentahydro-β-carbolinium ion intermediate might be the rate- and the enantioselectivity determining step.[3d]

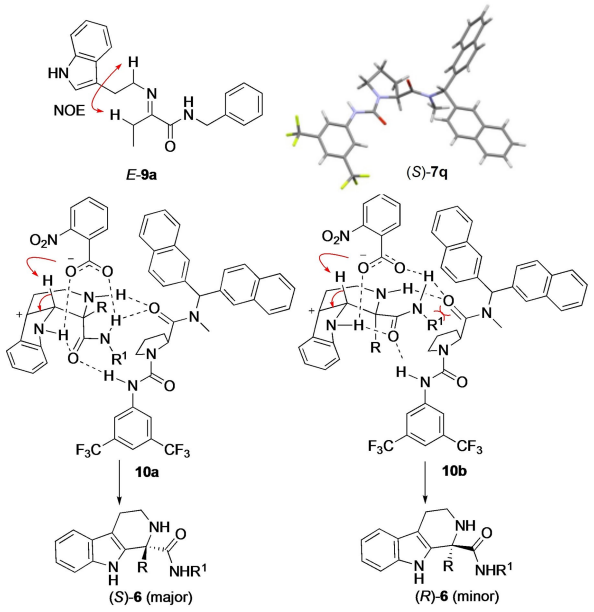
The *E*-geometry of the ketimine **9a** derived from **4a** and **5a** was determined on the basis of NOE studies. The X-ray structure of (*S*)-**7q**[21] indicates that the urea NH and the



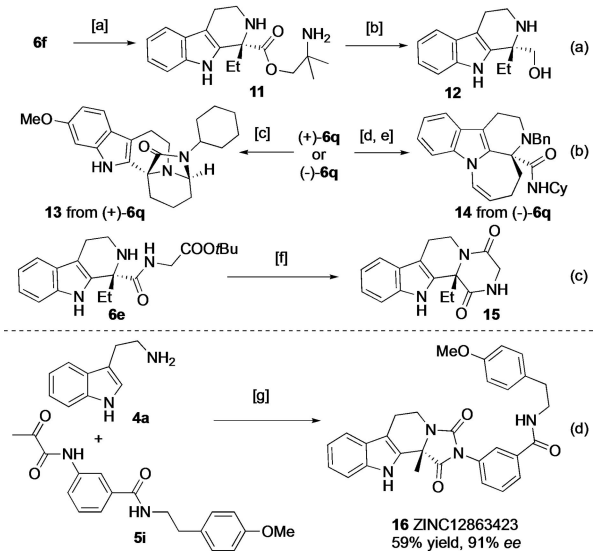
Scheme 6. Control experiments and KIE experiments.

amide oxygen is not, at least in solid state, engaged in an intramolecular H-bonding interaction. Since **7q** alone cannot catalyze the present PSR, we speculate that the reaction is initiated by protonation of the imine by *o*-nitrobenzoic acid and that the C–C bond forming event of the PSR might be reversible. A possible transition state **10a**, a ternary complex stabilized by a series of H-bonds and π–π interaction between the naphthalene unit of catalyst **7q** and *o*-nitrobenzoic acid, is proposed for the rearomatization step that leads to the major enantiomer (*S*)-**6** (Scheme 7). The alternative transition state **10b** suffers from more pronounced steric clashes and is therefore less favored. However, a more detailed study would be needed to elucidate precisely the catalytic activity and the stereochemical model of this reaction.

To illustrate the potential of this catalytic enantioselective PSR, some post-transformations were performed. Transesterification of **6f** under acidic conditions provided



Scheme 7. Speculative model for the observed enantioselectivity.



Scheme 8. Post-functionalization: [a] $CHCl_3$/conc HCl (v/v = 1:1), 80 °C, 70%. [b] LAH (1.0 equiv), THF, RT, 74%. [c] 4 N HCl in dioxane/H_2O (v/v = 1:1), RT, 96%. [d] K_2CO_3 (4.0 equiv), BnBr (5.0 equiv), DMF, 70 °C, 56%. [e] 4 N HCl in dioxane, THF/H_2O (v/v = 1:1), RT, 73%. [f] TFA (5.0 equiv), toluene, reflux, 74%. [g] standard PSR conditions, then CDI (4.0 equiv), NEt_3 (3.0 equiv), 100 °C, 59% yield, 91% *ee*. CDI = 1,1′-carbonyldiimidazole.

ester **11** which was further reduced to primary alcohol **12** (Scheme 8a). Treating (+)-**6q** with 4 N HCl in dioxane/H_2O afforded the pentacyclic compound **13**, a key structural motif found in peganumine A.[3e,4h,13] On the other hand, benzylation of (−)-**6q** followed by cyclization under acidic conditions furnished the tetracyclic enamine **14** (Scheme 8b). Intramolecular transamidation of **6e** occurred smoothly under acidic conditions to provide enantioenriched 2,5-diketopiperazine **15**, conformationally constrained dipeptide found in many natural products and drugs such as tadalafil (Scheme 8c).[23] Finally, asymmetric PSR of **4a** with **5i** followed by addition of CDI afforded ZINC12863423 (**16**), a potential inhibitor of translationally controlled tumor protein (TCPC),[24] in a one pot fashion.

In summary, we developed the first examples of catalytic enantioselective Pictet–Spengler reaction of tryptamines with α-ketoamides. The enormous success of (thio)urea-based catalysts is attributed to its ability to form two H-bonds with the substrates or with the counterion of the intermediate, activating and fixing therefore the three-dimensional structure of the transition state.[25] We demonstrate that simple prolyl-urea bearing a single NH bond donor function is an effective organocatalyst which exceeds the catalytic power of the classic dual H-bond donating (thio)urea catalysts in the Pictet–Spengler reaction of α-ketoamides.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Synthesis · Organocatalysis · Pictet–Spengler Reaction · Tetrahydrocarbazole · α-Oxoamides

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