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To cite this version:

Haiying Du, Yohan Dudognon, Jean Rodriguez, Thierry Constantieux, Xavier Bugaut. Weinreb β-Ketoamides in Enantioselective Organocatalysis: A Balance between Reactivity and Selectivity. SYNLETT, In press, 10.1055/s-0036-1591870 . hal-01723120

HAL Id: hal-01723120

https://hal.science/hal-01723120v1

Submitted on 5 Mar 2018

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Weinreb β-Ketoamides in Enantioselective Organocatalysis: a Balance between Reactivity and Selectivity

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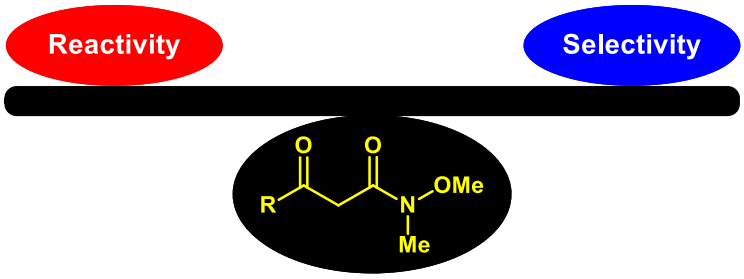


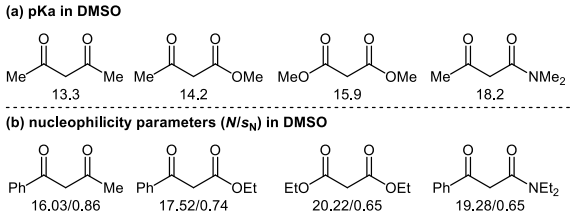
Abstract β-Dicarbonyl compounds have established themselves as substrates of choice in enantioselective organocatalysis because of their easy activation. Among them, β-diketones, β-diesters and β-ketoesters lead the dance and there has been only limited work with other β-dicarbonyl compounds as pronucleophiles. In this Synpacts article, we wish to discuss our recent contributions to the introduction of Weinreb β-ketoamides in organocatalyzed transformations, where they can provide an interesting balance between reactivity and selectivity, with also interesting potentialities in terms of post-functionalization.

1 Introduction
2 Preparation of Weinreb β-ketoamides
3 Michael addition to nitroolefins
4 Multicomponent synthesis of tetrahydropyridines
5 Outlook

Key words Dicarbonyl compounds, β-ketoamides, Michael additions, Multicomponent reactions, Organocatalysis, Regioselectivity, Stereoselectivity, Weinreb amides

1 Introduction

The early developments of organocatalysis and its mechanistic recognition are rooted in the origins of organic synthesis,[1] and it has occasionally been applied to the synthesis of enantioenriched compounds over the 20th century.[2] However, it is really at the turn of the century that a handful of key reports have created a deep impact on the community of synthetic chemists by the identification of how small chiral non-racemic molecules can catalyze transformations,[3] paving the way for numerous conceptual and practical developments.[4] Among the substrates that can be activated by organocatalysts, β-dicarbonyl compounds are especially interesting pro-nucleophiles.[5] Indeed, their tautomeric form is easily accessed and can add to a variety of electrophiles, either directly or after deprotonation to the corresponding enolate ion. In those transformations, interactions between the two carbonyl groups and the chiral catalyst can help in the construction of a well-defined transition state, ensuring high enantioselectivities. Even though diversified electrophiles have been used, it is quite surprising that the immense majority of pronucleophiles focused on β-diketones, β-diesters and β-ketoesters. The main reason for that, is probably their commercial availability and ease of activation thanks to relatively low pKa values (Scheme 1a).[6] On the contrary, other members of the family such as β-ketoamides generally need to be prepared and exhibit weaker acidities: for example, in DMSO, a pKa value of 14.2 was determined for ethyl acetoacetate, to be compared with 18.2 for *N*,*N*-dimethylacetoacetamide.[7] The reduced acidity generally translates in a more difficult activation by basic organocatalysts, but conversely the corresponding anions exhibit higher nucleophilicities (Scheme 1b).[8] In spite of these difficulties, interesting results have been obtained by us and other research groups for substrates in which the ketone function is included into a ring.[9] On the opposite, organocatalyzed reactions of linear β-ketoamides remain very limited.[10] As Weinreb amide are generally more acidic than other tertiary amides, we hypothesized that linear Weinreb β-ketoamides could bring about an interesting alternative for transformations where β-ketoesters are reactive but not selective enough while the corresponding β-ketoamides lack reactivity. Moreover, the Weinreb amide functionality in the final product would be amenable to a wide array of post-transformations.[11]

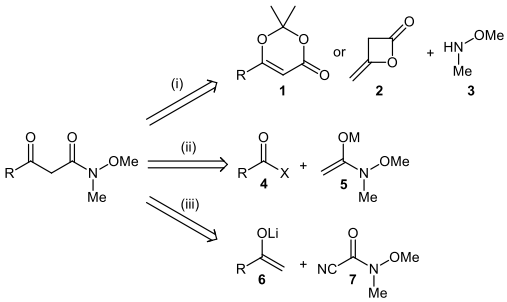


Scheme 1 Physico-chemical parameters of β-dicarbonyl compounds.

In this Synpacts article, we wish to provide a description of the recent work on the preparation of linear Weinreb β-ketoamides and their use as original pronucleophiles in enantioselective organocatalysis, where they can allow to reach an interesting equilibrium point between a good reactivity profile and original selectivities.

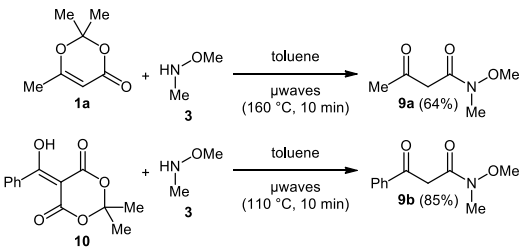
Preparation of Weinreb β-ketoamides

A prerequisite to develop new transformations on linear Weinreb β-ketoamides was to be able to prepare diversified substrates. Traditionally, such compounds have been prepared following three main strategies (Scheme 2): (i) the thermal decomposition of diketene (**1**) or 1,3-dioxin-4-one derivatives **2** in the presence of *N*,*O*-dimethylhydroxylamine (**3**);[12] (ii) the acylation of *N*-methoxy-*N*-methylacetamide's enolates **5**;[13] (iii) the trapping of Mander's type *N*-methoxy-*N*-methylcyanoformamide (**7**) with lithium enolates **6**.[14]



Scheme 2 Different Strategies for the synthesis of β-ketoamides.

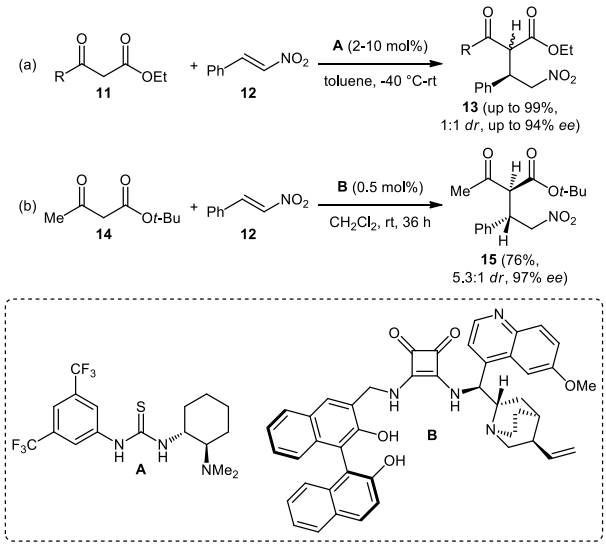
In view of the beneficial effect of microwave heating on Wolff rearrangements for the synthesis of a diversity of β-ketoamides,[15] we became interested in applying this method to other reactions of decomposition. Pleasingly, microwave heating of both 2,2,6-trimethyl-1,3-dioxin-4-one (**1a**) and 5-benzoyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**10**) in the presence of *N*,*O*-dimethylhydroxylamine (**3**)[16] afforded the corresponding Weinreb β-ketoamides **9a** and **9b** in good yields (Scheme 3).[17]



Scheme 3 Synthesis of Weinreb β-ketoamides under microwave heating.

3 Michael addition to nitroolefins

Nitroolefins are excellent electrophiles and have established themselves as substrates of choice in enantioselective organocatalysis.[18] In 2003, the group of Takemoto reported the Michael addition of β-dicarbonyl compounds to nitroolefins in the presence of a chiral bifunctional thiourea **A** bearing a pendant tertiary amine.[19] Two models have been proposed to explain the activation and the stereoselectivity, involving hydrogen bonding of the thiourea either with the nitroolefin[20] or with the β-dicarbonyl compound.[21] A limitation of this transformation is found when linear β-ketoesters **11** are used in combination with nitrostyrene (**12**). Indeed, the corresponding Michael adducts **13** were obtained with good yields and enantioselectivities, but with no diastereoselectivity, damaging the synthetic usefulness of the transformation (Scheme 4a).[20] Other related studies brought similar observations,[22] and monitoring of *dr* over time showed that some catalyst-controlled diastereoselectivity could be achieved during carbon-carbon bond formation. However, rather fast base-catalyzed epimerization annihilated the diastereoselectivity.[17,22d] There is a single example of reaction with *tert*-butyl acetoacetate (**14**) in the presence of polyfunctional squaramide **B**, with product **15** reaching 5.3:1 *dr* (Scheme 4b).[23] The comparatively good diastereoselectivity could probably be ascribed to the low catalyst loading and the buffering effect of the phenolic groups that probably tame the overall basicity of catalyst **B**.

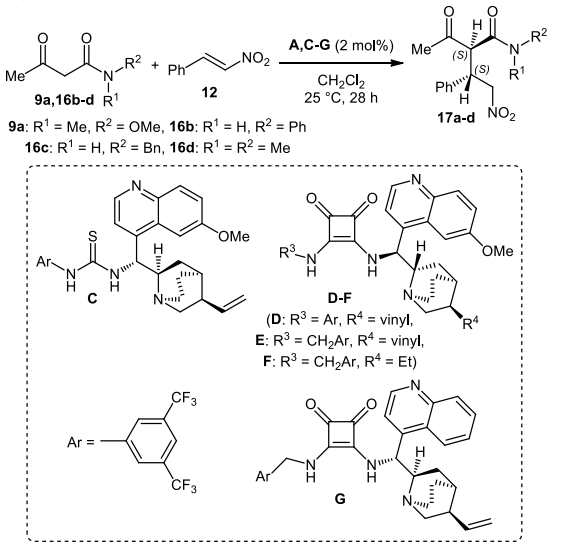


Scheme 4 Thiourea- or squaramide-catalyzed addition of β-ketoesters to nitrostyrene.

Based on these observations, we hypothesized that the reduced acidity of β-ketoamides could help preventing epimerization, opening possibilities for a completely stereoselective transformation. To test this hypothesis, diversely substituted β-ketoamides **9a,16b-d** were mixed with nitrostyrene (**12**) to afford Michael adducts **17a-d** (Table 1).[17] At first, different bifunctional hydrogen-bonding catalysts **A,C-G** were evaluated in the presence of Weinreb β-ketoamide **9a**. Takemoto catalyst **A** delivered the expected product **17a** but both diastereo- and enantioselectivities were disappointing (Entry 1), while quinine-derived thiourea **C** brought only marginal improvement (Entry 2).[24] We then turned our attention towards squaramide catalysts.[22a,25] Catalyst **D** bearing an aromatic substituent on the nitrogen atom of the squaramide moiety performed also poorly (Entry 3), in sharp contrast with those flanked with a benzylic substituent (Entries 4-6). Indeed, the three catalyst **E-G** delivered the expected product not only with high yields (94-99%) and enantiomeric excesses (95-98% *ee*), but also excellent diastereomeric ratios (15:1-17:1 *dr*). Moreover, reducing the reaction time to 14 h did not affect these results (Entry 7). Other substrates such as secondary β-ketoamides **16b-c** bearing either a phenyl or a benzyl group were also evaluated. In both cases, diastereoselectivity was very low (Entries 8,9). On the contrary, tertiary β-ketoamide **16d** could also be converted to the corresponding product **17d** with an excellent diastereoselectivity but a slightly reduced yield and slower kinetic (Entry 10). More generally, evaluation of the reaction rate

led to two conclusions:[17] (i) catalyst **E** is not only more selective than **D**, but also about 10 times faster; (ii) the reaction with β-ketoesters and secondary β-ketoamides is very fast, yet not diastereoselective, and the one with tertiary β-ketoamides much slower, while Weinreb β-ketoamide **9a** allows to find the best balance between reactivity and stereoselectivities.

Table 1 Evaluation of various β-ketoamides in the organocatalyzed Michael addition to nitroolefins.[17]

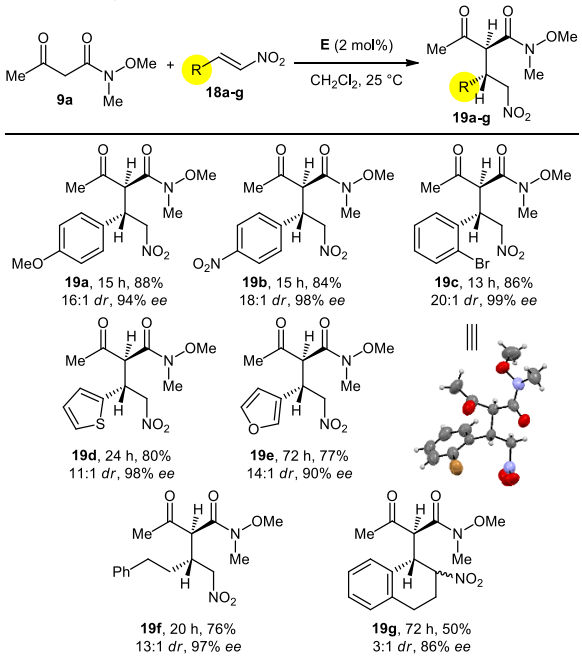


Entry	Substrate	Catalyst	Yield[a]	*dr*[b]	*ee*[c]
1	**9a**	**A**	97%	1:1	60%
2	**9a**	**C**	95%	3:1	83%
3	**9a**	**D**	91%	1:1	73%
4	**9a**	**E**	99%	16:1	98%
5	**9a**	**F**	94%	17:1	98%
6[d]	**9a**	**G**	97%	15:1	95%
7[e]	**9a**	**E**	92%	18:1	98%
8[d]	**16b**	**G**	73%	2:1	95%
9[d]	**16c**	**G**	78%	2:1	69%
10[f]	**16d**	**E**	84%	>20:1	98%

[a] Yield of product isolated by flash chromatography. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Value for the major diastereomer determined by HPLC on chiral stationary phase. [d] The other enantiomer of the product was obtained. [e] Reaction time: 14 h. [f] Reaction time: 35 h.

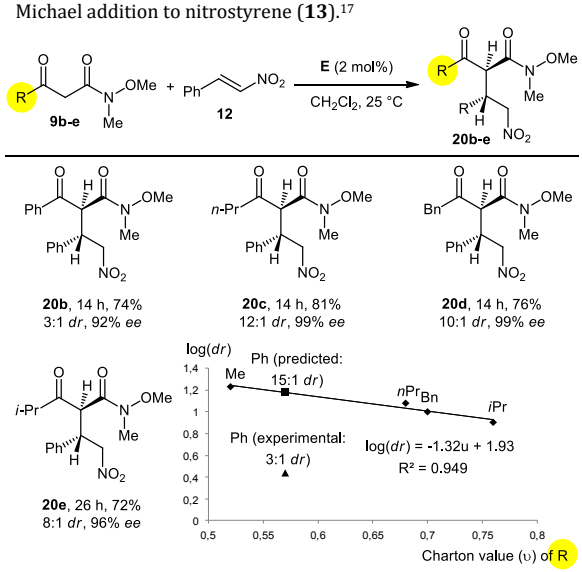
With the optimized reaction conditions in hand, Weinreb β-ketoamide **9a** was evaluated in the presence of various nitroolefins **18a-g** (Table 2). Irrespective of the electronic nature or positions of their substituents, all nitroolefins bearing a (hetero)aromatic group in β-position furnished the expected products **19a-e** in good yields and with excellent stereoselectivities. Both the absolute and relative configurations of product **19c** could be secured by analysis by X-ray diffraction, and the configurations of the other products were attributed by analogy. In addition to this, aliphatic nitroolefin **18f** and the trisubstituted one **18g** reacted with decent stereocontrol, the presence of diastereomers in **19g** being explained by an additional epimerizable stereocenter in α-position to the nitro group.[26]

Table 2 Scope of nitroolefins in the organocatalyzed Michael addition of β-ketoamide **9a**.[17]



Yield of product isolated by flash chromatography. *dr* determined by ^{1}H NMR spectroscopy of the crude reaction mixture. *ee* value for the major diastereomer determined by HPLC on chiral stationary phase.

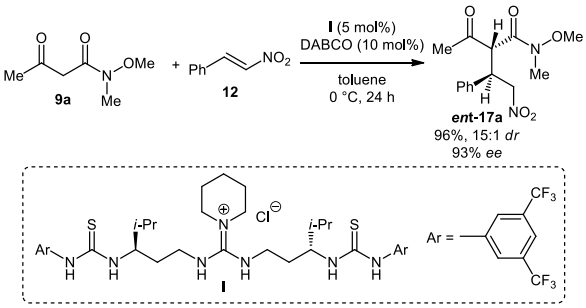
Table 3 Scope of Weinreb β-ketoamides in the organocatalyzed Michael addition to nitrostyrene (**13**).[17]



Yield of product isolated by flash chromatography. *dr* determined by ^{1}H NMR spectroscopy of the crude reaction mixture. *ee* value for the major diastereomer determined by HPLC on chiral stationary phase.

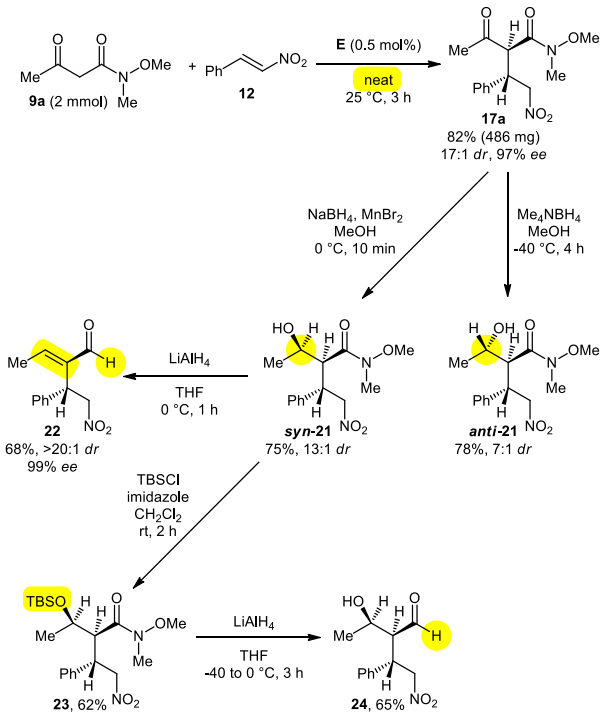
Conversely, nitrostyrene (**12**) was reacted with a series of Weinreb β-ketoamides **9b-e** to deliver the Michael adducts **20b-e** in good yields and with excellent enantiomeric excesses (Table 3). However, we could notice that the diastereomeric ratio decreased with the bulkiness of the substituent on the ketone side. For products **20a,c-e** bearing aliphatic substituents, a linear free-energy relationship (LFER) between log(*dr*) and the Charton steric parameter of the R was identified.[27] This observation, together with control experiments showed that the reaction is not reversible and no epimerization of the product can occur in the reaction conditions,[17] pointing towards a steric-dependent kinetic diastereocontrol, enabled by catalyst **E**. On the opposite, product **20b** containing an aromatic ketone does not follow the LFER showing that epimerization is not completely suppressed in that case.

Concomitantly with our studies, the group of Nagasawa reported a single example of the same reaction with β-ketoamide **9a** and nitrostyrene (**12**) in the presence of a guanidinium-bis-thiourea organocatalyst **I** and DABCO (Scheme 5).[28] In a similar fashion to our work, product ***ent*-17a** was obtained with a very high degree of control of both the diastereo- and the enantioselectivities, whereas the corresponding reaction with linear β-ketoesters was not diastereoselective.



Scheme 5 A related report by the group of Nagasawa.

Having shown that the replacement of β-ketoesters by Weinreb β-ketoamides was advantageous in their Michael additions to nitroolefins in terms of diastereoselectivity, we then wanted to exploit their synthetic potential (Scheme 6). At first, scale-up to half-gram scale proceeded uneventfully and offered the possibility to carry out the reaction in neat conditions and to decrease both the catalyst loading to 0.5 mol% and the reaction time to 3 hours. In terms of post-functionalization, the diastereoselective reduction of the ketone function of **17ad** into the corresponding alcohols **21** would deliver highly functionalized stereotriads. Pleasingly, $NaBH_4$ in the presence of a Lewis acid enabled a *syn* reduction with a high level of diastereocontrol (13:1 *dr*).[29] *Anti* reduction was more challenging but could finally be achieved with moderate diastereoselectivity (7:1 *dr*) by using Me_4NBH_4 as a bulky hydride donor at low temperature.[30] Weinreb amides have become popular substrates in organic synthesis because of their tendency to undergo selectively mono-additions of hydrides or organometallic reagents, contrary to other carboxylic acid derivatives such as esters.[11] Treatment of ***syn*-21** with $LiAlH_4$ actually reduced the amide function into the corresponding aldehyde, but was also accompanied by dehydration. Although this transformation destroys two stereocenters, it is still synthetically interesting as enal **22** could be seen as the product of a formal Rauhut-Currier reaction between crotonaldehyde and nitrostyrene, a reaction for which no enantioselective variant existed at that time.[31] Protection of the alcohol function as a silyl ether followed by the reduction of **23** delivered β-hydroxyaldehyde **24** with a moderate yield. We currently work on the application of the overall synthetic sequence to the synthesis of natural products.



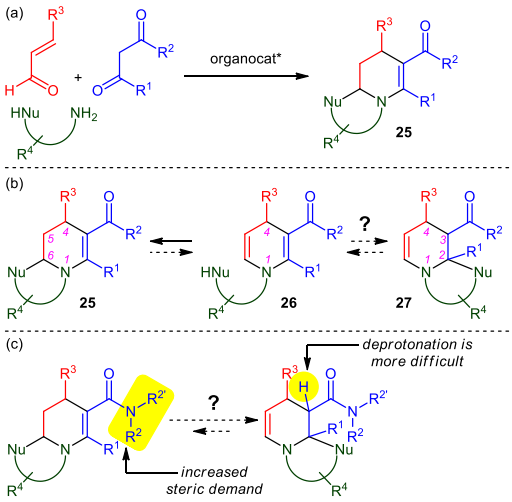
Scheme 6 Scale-up and post-functionalization of Michael adducts.[17]

4 Multicomponent synthesis of tetrahydropyridines

With this first successful application of Weinreb β-ketoamides in organocatalysis, we wondered whether they could also replace advantageously the corresponding β-ketoesters in other transformations.

Multicomponent reactions (MCRs) consist in a transformation where three or more reaction partners are assembled to form a single product that retains most atoms of the starting materials.[32] They represent extremely powerful tools for the synthesis of polyheterocyclic structures.[33] MCRs generally rely on the use of polyfunctional substrates bearing at the same time electrophilic and nucleophilic positions allowing to link the other reaction partners. For this reason, β-dicarbonyl compounds are especially appealing candidates for MCRs,[34] and organocatalysis an efficient tool to control their enantioselectivities.[35] A typical strategy is to combine a β-dicarbonyl compound, an α,β-unsaturated carbonyl compound and an amine bearing a pendant nucleophile to obtain 1,4,5,6-tetrahydropyridines **25** (Scheme 7a).[36] We became intrigued in the possibility to reverse the regioselectivity of the final cyclization from intermediate 1,4-dihydropyridines **26** to prepare regioisomeric 1,2,3,4-tetrahydropyridines **27**.(Scheme 7b).[37] A careful analysis of the structures of **25** and **27** reveal that the former one is likely to be more stable since its enamine

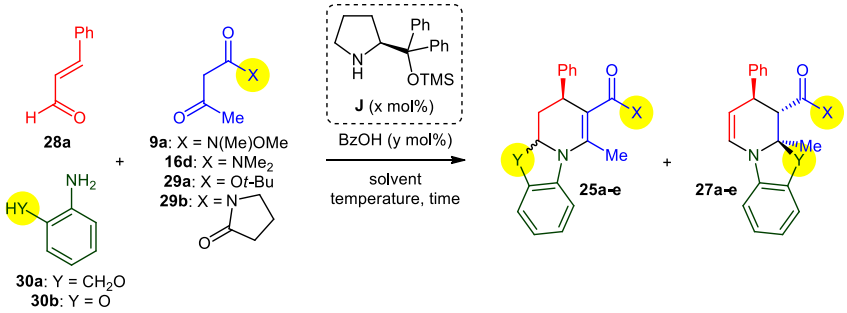
moiety is conjugated with the carbonyl compound, which is not the case for **27**. Disfavoring the conjugation should then help to drive the reaction towards the formation of **27**. Our working hypothesis was that this could be achieved by using a β-ketoamide, whose increased pKa value and steric demand would both play against conjugation (Scheme 7c).



Scheme 7 Synthesis of tetrahydropyridines via organocatalyzed enantioselective MCRs

To test our hypothesis, we embarked on the evaluation of several β-dicarbonyl compounds (**9a**, **16d** and **29a,b**) and bis-nucleophiles **30a,b** in combination with cinnamaldehyde (**28a**) and Hayashi-Jørgensen catalyst **J** (Table 4).[38] The catalyst controls the enantioselectivity of the initial Michael addition by the formation of a transient chiral iminium ion. The potential formation of regioisomeric products **25a-e** and **27a-e** was evaluated, along with their diastereomeric ratios and enantiomeric excesses. Starting with *tert*-butyl acetoacetate (**29a**) and 2-aminobenzyl alcohol (**30a**) in $C_6H_5CF_3$ at 0 °C for 48 h, only the 1,4,5,6-tetrahydropyridine **25a** was obtained as a mixture of diastereomers and with acceptable enantioselectivity (Entry 1). Using 2-aminophenol (**30b**) as the bis-nucleophile delivered the two regioisomers **25b** and **27b** (Entry 2). Pleasingly, the latter product was isolated as a single diastereomer and with 94% *ee*. Switching to Weinreb β-ketoamide **9a** opened the possibility for a complete regiocontrol (Entry 3): indeed, only the 1,2,3,4-tetrahydropyridine **27c** was observed, once again without any contamination from other diastereomers.[40] A thorough optimization study was initiated to improve the yield of product.[39] Using CH_2Cl_2 as the solvent improved it slightly (28% yield) and allowed to verify that the reaction was highly enantioselective (93% *ee*, Entry 4). Adding BzOH as a co-catalyst allowed to reach a similar yield with a halved reaction time (Entry 5). Increasing the reaction temperature to 10 °C and doubling the catalysts' loadings allowed to isolate **27c** in 60% yield, with >20:1 *dr* and 94% *ee* (Entry 6).

Table 4 Evaluation of various β-dicarbonyl compounds and bis-nucleophiles for the synthesis of enantioenriched 1,2,3,4-tetrahydropyridines through an organocatalyzed MCR.[39]



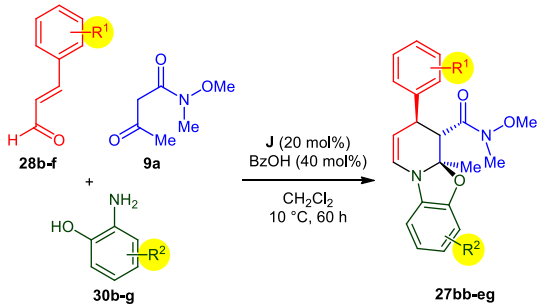
Entry	Substrates	x	y	Solvent	Temperature (°C)	Time (h)	Products (Yield[a], *dr*[b], *ee*[c])
1	**29a, 30a**	10	0	$C_6H_5CF_3$	0	48	Only **25a** (27%, 1.3:1, 88%)
2	**29a, 30b**	10	0	$C_6H_5CF_3$	0	48	**25b** (12%, 1.5:1, nd[d]) and **27b** (25%, >20:1, 94%)
3	**9a, 30b**	10	0	$C_6H_5CF_3$	0	48	Only **27c** (19%, >20:1, nd[d])
4	**9a, 30b**	10	0	CH_2Cl_2	0	48	Only **27c** (28%, >20:1, 93%)
5	**9a, 30b**	10	20	CH_2Cl_2	0	24	Only **27c** (32%, >20:1, 95%)
6	**9a, 30b**	20	40	CH_2Cl_2	10	60	Only **27c** (60%, >20:1, 94%)
7	**9a, 30b**[e]	20	40	CH_2Cl_2	10	60	Only **27c** (50%, >20:1, 72%)
8	**16d, 30b**	20	40	CH_2Cl_2	10	60	Only **27d** (29%, >20:1, 92%)
9	**29b, 30b**	20	40	CH_2Cl_2	10	60	Complex mixture containing **25e** and **27e**

[a] Yield of product isolated by flash chromatography. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Value for the major diastereomer determined by HPLC on chiral stationary phase. [d] Not determined. [e] Sequential reaction conditions: 2-aminophenol was added after 48 h of reaction.

Assuming that the loss of yield could be attributed to the formation of unproductive imine and enamine derivatives, we tried to perform at first the enantioselective Michael addition and to add 2-aminophenol (**30b**) later (Entry 7). Not only the yield was not improved but there was also a strong decrease of the enantiomeric excess. This result highlights an interesting feature of domino and multicomponent reactions, in which potentially sensitive reaction intermediates can be transformed to more stable products before racemization and/or degradation. Tertiary β-ketoamide **16d** also afforded 1,2,3,4-tetrahydropyridine **27d** with excellent regio- and stereoselectivities but in only 29% yield (Entry 8), while pyrrolidinone-derived β-ketoamide **29b** resulted in a non-regioselective and sluggish reaction (Entry 9). All these observations once again indicate that Weinreb β-ketoamides present an interesting profile to reach a compromise between reactivity and selectivity.

With these optimized reaction conditions in hands, Weinreb β-ketoamide **9a** was placed in the presence of substituted enals **28b-f** and 2-aminophenols **30b-g** to deliver products **27bb-eg** in moderate yields as only one regio- and stereoisomer, with enantiomeric excesses ranging from 82% to 96% (Table 5). Both the yields and enantiomeric excesses tended to increase when more electron-deficient enals where used (Entries 1-5). On the opposite, the electronic nature of the substituent on the 2-aminophenol had only a limited influence on the reaction outcome (Entries 6-9), with 3-aminonaphth-2-ol (**30g**) giving the best *ee* (Entry 10).

Table 5 Scope of substituted enals and 2-aminophenols in the organocatalyzed synthesis of 1,2,3,4-tetrahydropyridines.[39]

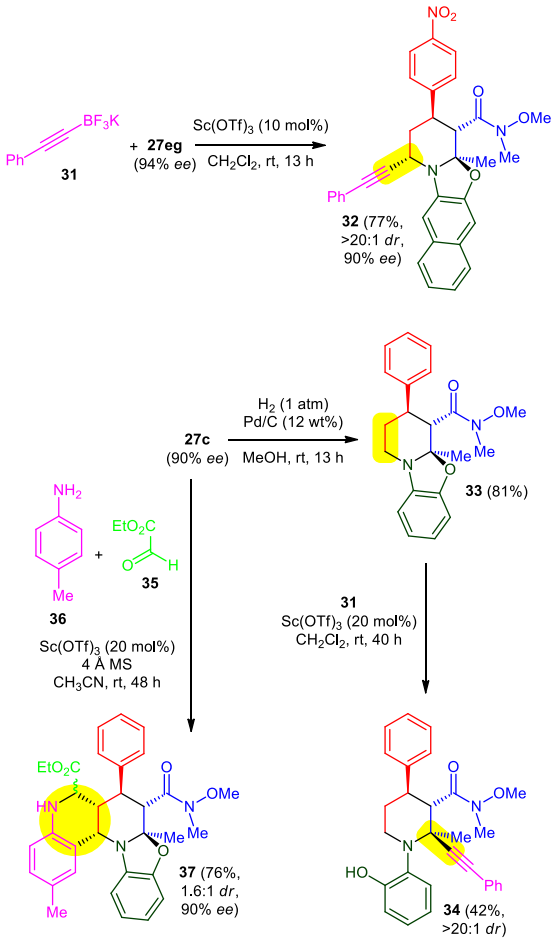


Entry	Enal (R^1)	2-Aminophenol (R^2)	Yield[a]	*ee*[b]
1	**28b** (4-MeO)	**30b** (H)	41%	82%
2	**28c** (4-F)	**30b** (H)	45%	86%
3	**28d** (4-Cl)	**30b** (H)	48%	90%
4	**28e** (4-NO_2)	**30b** (H)	50%	94%
5	**28f** (3-Cl)	**30b** (H)	49%	94%
6	**28e** (4-NO_2)	**30c** (4-Cl)	43%	90%
7	**28e** (4-NO_2)	**30d** (5-Cl)	41%	92%
8	**28e** (4-NO_2)	**30e** (3-Me)	45%	90%
9	**28e** (4-NO_2)	**30f** (5-Me)	45%	92%
10	**28e** (4-NO_2)	**30g** (4,5-$(CH)_4$)	55%	96%

[a] Yield of product isolated by flash chromatography. For all products, *dr* determined by ^{1}H NMR spectroscopy of the crude reaction mixture was >20:1. [b] Value for the major diastereomer determined by HPLC on chiral stationary phase.

An interesting feature of 1,2,3,4-tetrahydropyridines of type **27** is that they bear a potentially reactive enamine function (Scheme 8). In the presence of a Lewis acid such as $Sc(OTf)_3$, the resulting iminium ion could be trapped by a nucleophile. For example, the combination of **27eg** with potassium phenylethynyltrifluoroborate (**31**) delivered highly substituted piperidine **32** in good yield, as a single diastereomer and with only a minor erosion of the enantiomeric excess (from 94% to 90%).[40,41] Catalytic hydrogenation of the enamine is also straightforward as illustrated with the formation of piperidine **33** in good yield from **27c**. It is then possible to reveal the reactivity of the *N,O*-acetal that can open to the corresponding iminium ion, also in the presence of $Sc(OTf)_3$. Once again using **31** as the nucleophile resulted in the diastereoselective formation of **34** in moderate yield. The enamine function can also participate as an electron-rich 2π-partner in an inverse-demand hetero-Diels-Alder reaction: the Povarov reaction with the imine formed *in-situ* from ethyl glyoxylate (**35**) and *p*-anisidine (**36**) afforded the polycyclic structure **37** without any racemization.[42] The two new stereogenic centers on the central piperidine ring are fully controlled, but not the one α to the ester function, resulting in the existence of two diastereomers.[40]

Scheme 8 Post-functionalization of 1,2,3,4-tetrahydropyridines.[39]



Outlook

In this Synpacts article, we wished to highlight how the specific electronic and steric properties of linear Weinreb β-ketoamides can influence their behavior in organocatalyzed enantioselective transformations. They occupy a special position halfway between β-ketoesters and other β-ketoamides, which allow to find a fine balance between reactivity and selectivity. Their unique features could be exemplified by the control of *diastereoselectivity* in their Michael addition to nitroolefins in the presence of a bifunctional hydrogen-bonding catalyst,[17] and the reversal of *regioselectivity* in the preparation of tetrahydropyridines through a MCR with iminium activation.[39] We strongly believe that their systematic evaluation in organocatalyzed transformations involving β-dicarbonyl compounds as substrates will result in other important findings in the near future.

Funding Information

Financial support from Aix Marseille Université, Centrale Marseille and the CNRS, along with scholarships from the China Scholarship Council (H.Y.D.) and the Ministère de l'Enseignement Supérieur et de la Recherche (Y.D.) are acknowledged.

Acknowledgment

We warmly thank Dr. Nicolas Vanthuyne and Marion Jean for HPLC analyses on chiral stationary phase, and the whole team of the Spectropole (www.spectropole.fr) for NMR and MS analyses.

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Biosketches

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