Organocatalysis

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1,2-Dicarbonyl Compounds as Pronucleophiles in Organocatalytic Asymmetric Transformations

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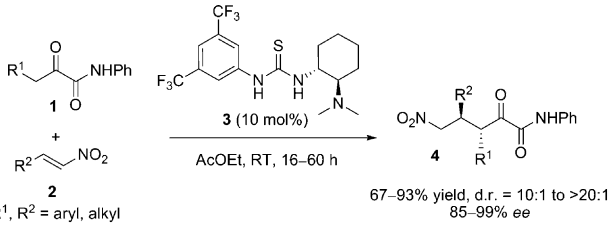
1,2-dicarbonyls · asymmetric catalysis · domino reactions · organocatalysis · pronucleophiles

Since the first preparation of an α-ketoacid in 1835 by Berzelius,[1] 1,2-dicarbonyl derivatives became very popular and particularly attractive synthetic scaffolds given their dense number of reactive centers that can be exploited in successive reactions or in cascade sequences. Especially the synthesis of chiral α-ketoesters has raised a wide interest in total synthesis of natural products.[2] However, utilization of 1,2-dicarbonyl compounds in asymmetric organocatalytic transformations was mostly limited to the increased electrophilic ketone reactivity by the presence of an adjacent carbonyl group.[3] This highlights the importance of the development of suitable selective organocatalyzed activation modes for enhancing the nucleophilic potential of 1,2-dicarbonyl compounds towards cross-condensation[4] instead of competitive useless self-condensation.

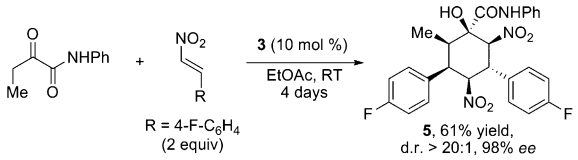
This challenge was first met in 2004, by Yamamoto and co-workers with one single example of an organocatalytic asymmetric cross-aldol reaction of ethyl pyruvate and chloral by enamine activation with a proline-tetrazole catalyst assisted by water.[5,6] A more general highly diastereo- and enantioselective organocatalytic α-functionalization by Michael addition of various 1,2-ketoamides **1** to nitroolefins **2**



Scheme 1. Enantioselective conjugate addition with 1,2-ketoamides.

was introduced in 2010 (Scheme 1).[7a] In this case, non-covalent hydrogen-bonding activation by catalyst **3** turned out to be the most efficient, combined with the cooperative participation of the amide N–H moiety, which was found to be crucial for both the reactivity and the selectivity. Synthetically valuable *anti*-adducts **4** were obtained in good yields and very high diastereo- and enantioselectivities.

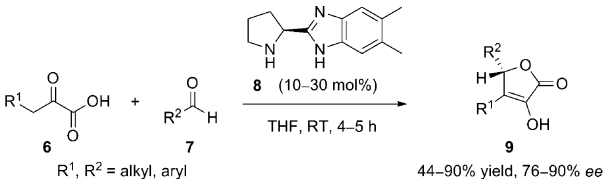
An illustration of the versatile reactivity of these chiral 1,2-dicarbonyl compounds, combining both nucleophilic and electrophilic characteristics, is a pseudo three-component domino Michael/Michael/Henry reaction affording the hexa-substituted cyclohexane **5** with the creation and control of six stereogenic centers in one synthetic operation (Scheme 2).[7a]



Scheme 2. Diastereo- and enantioselective domino cyclization.

This ambident reactivity of 1,2-dicarbonyl compounds in a domino enantioselective organocatalytic transformation was pioneered by Dondoni et al. in 2005.[8a] They disclosed an efficient access to enantiomerically enriched isotetronic acid by an homoaldol reaction of ethyl pyruvate catalyzed by (*S*)-(+)-1-(2-pyrrodinylmethyl)pyrrolidine in combination with trifluoroacetic acid as co-catalyst. A more general one-pot enantioselective aldolization-lactonization sequence between α-oxocarboxylic acids **6** and various aldehydes **7** with a benzimidazole proline-derived organocatalyst **8** was reported three years later by Landais and co-workers for the synthesis of various isotetronic derivatives **9** (Scheme 3).[8b]

1,2-Diketones have also been shown to be excellent nucleophilic partners in organocatalyzed domino transformations. Moreover, they are particularly prone to further react through their electrophilic character in subsequent transformations because of higher reactivity compared to the



Scheme 3. Enantioselective synthesis of isotetronic acids.

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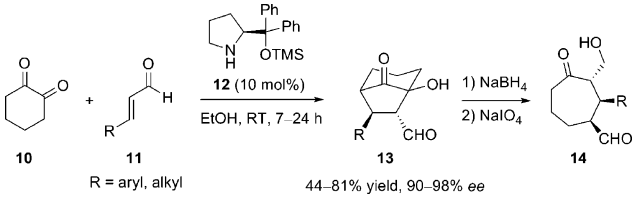
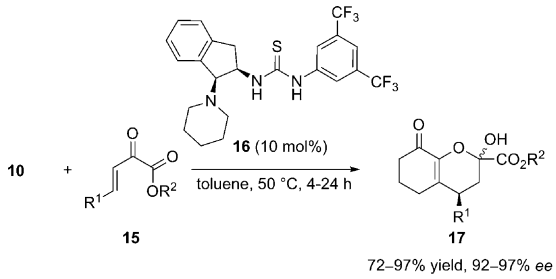
corresponding 1,2-ketoesters or amides. This was first achieved elegantly by Rueping et al. in 2009, who reported an asymmetric organocatalytic domino Michael/aldol reaction, by enamine/iminium activation with catalyst **12**.[9] Polyfunctionalized bicyclo[3.2.1]octanes **13** were obtained in good yields and excellent enantioselectivities from cyclohexan-1,2-dione (**10**) and α,β-unsaturated aldehydes **11** and were easily converted to trisubstituted seven-membered ring **14** without loss of the enantiomeric excess (Scheme 4).



Scheme 4. Enantioselective Michael/aldol domino reaction.

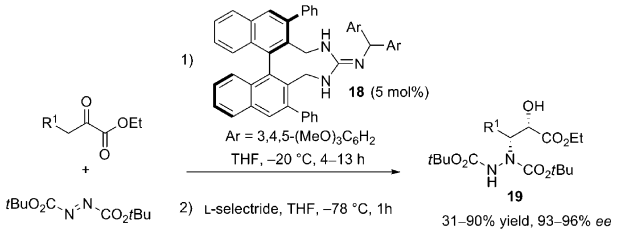
Shortly after, the same group and Zhao and co-workers independently reported a similar cascade reaction with nitroalkenes as electrophiles under bifunctional hydrogen-bonding catalysis.[10] This enantioselective domino Michael/Henry reaction afforded the same bicyclo[3.2.1]octane cores albeit with somewhat lower diastereoselectivity. Interestingly, α-substituted nitroalkenes could be employed affording bicyclic structures with two adjacent quaternary stereogenic centers with excellent selectivities. Following these results, Wang and co-workers showed that diketone **10** could also be used as dual C–O dinucleophile towards α,β-unsaturated pyruvates **15** acting as dual electrophiles (Scheme 5).[11] Thus,



Scheme 5. Enantioselective cascade Michael/enolization/cyclization.

they developed an enantioselective domino Michael/enolization/cyclization sequence catalyzed by a chiral indane-skeleton-based thiourea **16** for the synthesis of valuable dihydro-2*H*-pyranes **17** in high yields and with excellent enantioselectivities.

Finally, besides this opening towards the organocatalytic enantioselective formation of C–C bonds, the first C–N bond that involves 1,2-ketoesters as pronucleophiles was only proposed very recently by Terada et al. for the α-amination using an axially chiral guanidine base **18** (Scheme 6).[12] The reaction is quite general and can be applied to a range of 1,2-ketoesters giving, after reduction, the *syn*-α-hydroxy-β-hydrazinoesters **19** with always good enantioselectivities. The authors noted an important influence of the steric hindrance around the reactive nucleophilic center and lower yields were observed with secondary alkyl-substituted α-ketoesters.



Scheme 6. Enantioselective α-amination of 1,2-ketoesters.

These recent contributions serve to highlight the synthetic power of 1,2-dicarbonyl compounds as pronucleophiles using specific organocatalytic activation modes. Organic chemists have for a long time uncovered the synthetic usefulness of the 1,3-dicarbonyl homologues, but 1,2-dicarbonyl compounds were, in comparison, underexploited and mainly used as activated ketones for difficult transformations. Nowadays, they proved particularly efficient, in sequential and domino transformations leading to various functionalized optically active targets including five-, six-, and seven-membered ring systems by formation of C–C or C–N bonds. The last two years have witnessed the emergence of new powerful methodologies involving α-oxocarbonyl compounds as pronucleophiles but this field of research is still in its infancy and many other ingenious developments should appear shortly.

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[1] J. J. Berzelius, *Ann. Phys.* **1835**, *36*, 1.
[2] D. Enders, M. H. Bonten, G. Raabe, *Synlett* **2007**, 885.
[3] For selected examples of utilization of 1,2-dicarbonyl compounds as electrophiles in organocatalytic transformations, see: a) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732; b) B. Procuranti, S. J. Connon, *Chem. Commun.* **2007**, 1421; c) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková, P Kočovsky, *Org. Lett.* **2007**, *9*, 5473; d) V. B. Gondi, K. Hagihara, V. H. Rawal, *Chem. Commun.* **2010**, *46*, 904.
[4] Their nucleophilicity was pioneered by Jørgensen and co-workers with transition-metal catalysis using chiral bisoxazoline–copper(II) complexes : a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995; b) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420; c) for recent complementary studies in this field, see: G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2008**, *120*, 6953; *Angew. Chem. Int. Ed.* **2008**, *47*, 6847; Y. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2009**, *121*, 3403; *Angew. Chem. Int. Ed.* **2009**, *48*, 3353.
[5] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.
[6] For asymmetric aldolization with pyruvic aldehyde dimethyl acetal as a masked 1,2-dicarbonyl compound catalyzed by (*S*)-proline, see: D. Enders, T. Gasperi, *Chem. Commun.* **2007**, 88.
[7] a) O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246; b) for

utilization of mono- or dinuclear chiral nickel complexes as catalysts, see: A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036; Y. Xu, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2010**, *12*, 3246.

[8] a) P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657; b) J.-M. Vincent, C. Margottin, M. Berlande, D. Cavagnat, T. Buffeteau, Y. Landais, *Chem. Commun.* **2007**, 4782.

[9] M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem.* **2009**, *121*, 3754; *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.

[10] a) M. Rueping, A. Kuenkel, R. Frölich, *Chem. Eur. J.* **2010**, *16*, 4173; b) D. Ding, C.-G. Zhao, Q. Guo, H. Arman, *Tetrahedron* **2010**, *66*, 4423.

[11] a) Q. Ren, Y. Gao, J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 5297; b) for a previous similar sequence using 2-hydroxy-1,4-naphthoquinone that can be regarded as a 1,2-diketone type pronucleophile, see: M. Rueping, E. Sugiono, E. Merino, *Angew. Chem.* **2008**, *120*, 3089; *Angew. Chem. Int. Ed.* **2008**, *47*, 3046.

[12] M. Terada, K. Amagai, K. Ando, E. Kwon, H. Ube, *Chem. Eur. J.* **2011**, *17*, 9037. (Corrigendum: M. Terada, K. Amagai, K. Ando, E. Kwon, H. Ube, *Chem. Eur. J.* **2011**, *17*, 9858.)

