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Design and Application of 2,2-Dibromodimedone as Organic Brominating Reagent for Asymmetric Bromination of 1,3-Dicarbonyl Compounds and Ketones Catalysed by Chiral Amino Acids

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Abstract: A green and ecofriendly enantioselective α-bromination of carbonyl and 1,3-dicarbonyl compounds is reported involving the synthesis of a novel organic brominating source. The organic brominating reagent can be recovered after each cycle, rebrominated and reused. The reaction is catalysed by chiral amino acids and completed within a short reaction time with good enantioselectivity and exclusive formation of only α-monobrominated carbonyl compounds.

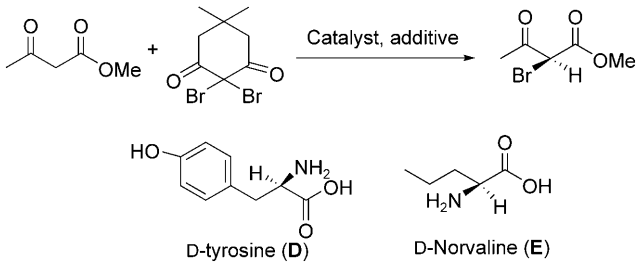
Keywords: brominating reagent; α-bromination; chirality; 1,3-dicarbonyl compounds; enantioselectivity

Oganocatalytic asymmetric carbon-halogen bond formation reactions have been considerably less exploited[1] as compared to other carbon-heteroatom bonds.The importance of these asymmetric halogenated compounds lies in the fact that these functional groups serve as versatile motifs for further synthetic operation.[2] Moreover, they are precursors of innumerable biologically active drugs and and compounds for material sciences.[3] Furthermore, the enantioselective halogenation of bioactive compounds like amino acids also has the advantage of improved chemical and metabolic stability.[4] Accordingly, the stereoselective synthesis of carbon-halogen compounds has invoked interest among chemists and various novel strategies have been reported.[1a,4a] The construction of stereocontrolled C–F, C–Br and C–I bonds is mainly concentrated on carbonyl compounds as the substrates, with an electrophilic halogenating reagent[5] in the presence of a chiral catalyst.

The cruicial step in the stereoselective halogenation of carbonyl compounds is the proper choice of the catalyst along with the halogenating reagent to obtain optimum enantioselectivity, since the degree of enantioselectivity is governed by both the halogenating reagent as well as the catalyst. On this line, Selectfluor,[6] *N*-fluorobenzenesulfonimide (NFSI),[7] has been reported as a organic fluorinating reagent while chlorinated quinolinone,[8,6a] trichloroquinolinone[9] and brominated quinine derivatives,[10] as well as 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone[11] are reported as the organic chlorinating and brominating sources, respectively. Reports on stereoselective iodination are scarce,[11a] whereby *N*-iodosuccinimide was used as the organoiodo reagent. Additionally, Yamamoto et al.[12] have designed a chlorinated chiral 1,3-dicarbonyl compound and investigated its application for enantioselective chlorinations of silyl enolates. Besides, the literature also documents[13] the chlorination and bromination of β-keto esters catalysed by Ti(TADDOLato) complexes with NCS and NBS. However the α-bromo-β-keto esters obtained by this protocol gave very low selectivity as NBS possesses the ability to brominate the substrate, even without the added assistance of a catalyst. Regardless of the reported procedure, there still exists a demand for an effective organic brominating reagent with the aim of obtaining better stereoselectivity.

In this communication, we wish to report a novel organic brominating agent for the enantioselective α-bromination of carbonyl and 1,3-dicarbonyl compounds with D-norvaline as catalyst and pyridinedicarboxylic acid as additive as shown in Scheme 1

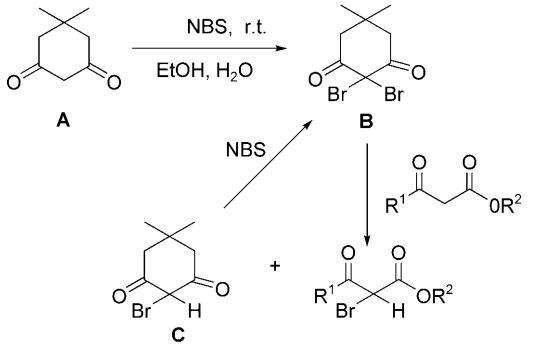
Another fact to be taken into account is that there is always a competition for the uncatalysed bromination of the enol form of the 1,3-dicarbonyl compounds against the catalysed stereoselective version, even at



Scheme 1. Organocatalytic asymmetric α-bromination of 1,3-dicarbonyl compounds and ketones.

low temperature. This is a major setback, affecting the stereoselectivity of the synthesised halogenated compounds. In order to overcome this shortcoming, our initial goal was to design a brominating reagent which would be less reactive with the aim of inhibiting the background reactions. We envisaged that the background reaction could be controlled, if the reaction conditions are so tuned that the bromonium ion should be released from the reagent only with the exclusive assistance of the catalyst.

We speculated that a dibrominated cyclic 1,3-dicarbonyl compound will be an effective organic brominating source based on its tendency for the facile loss of one bromine atom in the presence of an acid. Accordingly, we have chosen to di brominate a cyclic β-carbonyl compound, namely 5,5- dimethylcyclohexa-1,3-dione (**A**) which will act as a bromine source in the presence of a chiral catalyst for the stereoselective α-brominations of unsymmetrical carbonyl and 1,3-dicarbonyl compounds. Hence **A** was converted to 3,3-dibromo-5,5-dimethylcyclohexa-1,3-dione (**B**) using *N*-bromosuccinimide in an ethanol:water system as shown in Scheme 2. The compound (**B**) precipitated out of the solvent after the completion of the reaction within 1 hour. The compound was filtered, washed with water several times, dried and used as a source of bromine. **B** is converted to **C** after giving away a bromine atom, which could be further recycled to **B**



Scheme 2. Synthesis of the brominating reagent.

easily. The compound **B** is stable, easy to handle and can be stored for a long time without decomposition.

Thus, we investigated the application of **B** for the α-bromination of carbonyl compounds in the presence of catalytic amount of a chiral amino acid. Although chiral secondary amines have been well exploited to date, the organocatalytic application of chiral primary amines has been comparatively less exploited.[14] We envisaged that the primary amine will promote the *in situ* enamine formation from the 1,3-dicarbonyl compounds, thereby facilitating the stereosective bromination step. We initially started our investigation by screening the chiral primary amino acids D-tyrosine (**D**) and D-norvaline (**E**) as catalyst in various solvents in order to find the optimal reaction conditions.

Another important fact not to be overlooked is that the α-unsubstituted β-keto esters when subjected to bromination, always have a tendency to form α,α-dibromo esters in minor amounts along with the formation of α-monobromo compounds. Additionally, the halogenated compounds are prone for decomposition during purification through the silica column[15] giving remarkably low yields of the purified products. Considering the aforementioned facts, the target was to develop a protocol to obtain the monobrominated compounds exclusively, hindering the formation of dibromo compounds along with complete consumption of the starting materials. Accordingly, we tried to optimise the reaction conditions with the goal of obtaining α-monobrominated compounds selectively with excellent enantioselectivity. The optimisation of the reaction conditionsis shown in Table 1.

In this line, in an initial experiment, compound **B** was used to brominate methyl acetoacetate (**1a**) in acetonitrile using D-tyrosine as the catalyst. Although the reaction gave α-monobromomethyl acetoacetate, within 1 hour, the starting material was not consumed even after prolonging the reaction for 6 h. We envisaged that the reaction was sluggish as **B** is a weak brominating agent. Hence, we expected that the introduction of an acid (pyridinedicarboxylic acid) would increase the electrophilic character of **B** and accelerate the rate of bromination of the β-keto ester.[16] Moreover the enol form of the carbonyl compounds would be further favoured by the presence of acid.

To our delight, the reaction rate was increased dramatically under the influence of the acid, furnishing the α-bromomethyl acetoacetate within a span of 1 hour with the complete consumption of starting material. Among the screened catalysts, D-norvaline was found to be the most effective with pyridinedicarboxylic acid (PDA) as an additive in CH_2Cl_2 as solvent of choice at 0–5 °C for giving α-bromomethyl acetoacetate with excellent enantioselectivity. The compound **C** recovered after the reaction was further analysed by single crystal XRD.[17] The compound **C** was further brominated and reused.

Table 1. Optimisation of the enantioselective α-bromination of methyl acetoacetate.

Entry	Catalyst [10 mol%]	Solvent	Temp. [°C]	Acid [1 mol%]	Conversion [%] [starting:mono:di][a]	*ee* [%][b]
1	**D**	CH_3CN	r.t.	–	43:57:0	nd
2	**D**	CH_3CN	r.t.	PDA	0:87:13	nd
3	**D**	CH_3CN	0–5	PDA	0:100:0	75
4	**D**	THF	0–5	PDA	11:89:0	nd
5	**D**	Acetone	0–5	PDA	0:100:0	85
6	**E**	THF	0–5	PDA	0:100:0	79
7	**E**	CH_3CN	0–5	PDA	0:100:0	89
8	**E**	Acetone	0–5	PDA	9:81:0	nd
9	**E**	CH_2Cl_2	0–5	PDA	100	98

[a] The conversions were determined from ^{1}H NMR spectra.
[b] The enantioselectivity was determined by Chirasil Dex-CB GC column.

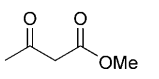
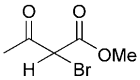
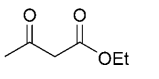
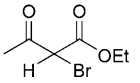
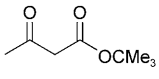
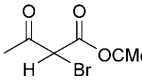
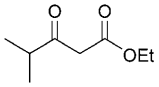
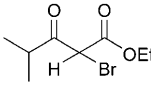
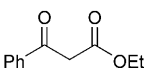
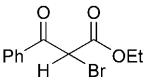
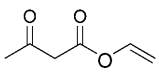
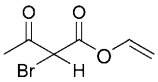
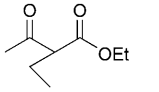
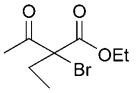
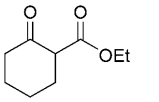
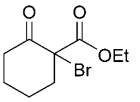
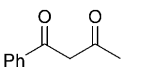
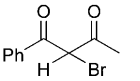
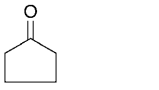
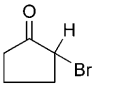
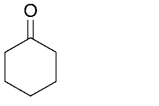
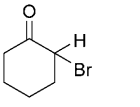
Encouraged by these results, we brominated a variety of unsymmetrical α-unsubstituted β-keto esters (Table 2, entry 1a–1e), which furnished α-bromo-β-keto esters **2a–2e** exclusively with good enantioselectivity.

Secondly, we tried to explore our protocol with a β-keto ester, allyl acetoacetate (Table 2, entry 1f) possessing a double bond with the aim to examine whether the active methylene is brominated while the olefin survives. The product **2f** was obtained solely without any formation of by-products like bromination of the double bonds. Next we diverted our attention to an acyclic and a cyclic α-substituted β-keto ester (Table 2, entry 1g and 1h). Both the acyclic and cyclic α-bromo-β-keto esters **2g** and **2h** showed excellent stereoselectivity along with good yield. Furthermore, the compound **2h** was assigned the *S*-configuration by comparing the specific rotation values with that reported in literature.[9] Next, we investigated the feasibility of brominating an unsymmetrical 1,3-diketone (Table 2, entry 1i) which is reported to be a remarkably challenging class of substrates.[14,10] In contrast, we obtained α-brominated benzoylacetone **2i** as the product with high stereoselectivity. Next we tried to broaden our investigation by examining some unsubstituted cyclic ketones (Table 2, entries 1j and 1k). The desired compounds **2j** and **2k** were obtained with considerably good enantioselectivity.

The asymmetric induction was due to D-norvaline, which probably formed a cyclic transition state with the enol form of the carbonyl compounds to form an enamino ester intermediate. This activation process is followed by the stereoselective electrophilic attack of bromine from **B** to form the C–Br bond in the substrate.[13] Since both the bromine atoms are equivalent, any one can be released to give the enantioselective brominated compound. Further mechanistic details are under investigation.

In conclusion. we have synthesised a novel and environmentally benign brominating reagent for the ef-

Table 2. Enantioselective α-bromination of 1,3-dicarbonyl and carbonyl compounds.

Entry	Substrate (**1**)	Product (**2**)	Yield [%][a,b]	Time [h]	*ee* [%][c]
a			90	1	98
b			92	1	99
c			90	1.5	99
d			89	1.5	92
e			85	3	98
f			91	2	96
g			88	2	95
h			94	1	98
i			95	1	96
j			90	3	97
k			91	3	97

[a] Yields refer to the isolated products.
[b] The compounds were characterised by NMR and mass spectrometry as well as elemental analyses.
[c] The enantioselectivity was determined on a Chirasil Dex-CB GC column immediately after isolation.

ficient asymmetric α-bromination of β-keto esters, cyclic ketones and 1,3-diketones with good enantioselectivity. The organic brominating reagent can be recovered and reused after each cycle. The technique of isolation of the pure products from the reaction mixture without column chromatography is a major asset of this protocol. We hope that the idea will contribute to the field of enantioselective bromination.

Experimental Section

Preparation of 2,2-Dibromo-5,5-dimethylcyclohexa-1,3-dione

To a clear solution of 5,5-dimethylcyclohexa-1,3-dione (1 mol, 1.4 g) in 20 mL of ethanol:water (15:5), was added NBS (2.1 mol, 1.95 g) (in portions) at room temperature. The solution becomes light yellow on addition of NBS. The reaction mixture was stirred vigorously at room temperature until the disappearance of the yellow colour.Another portion of NBS was added with the reappearance of the yellow colour. The addition of the total amount of NBS was completed after addition in four portions. The 2,2-dibromo-5,5-dimethylcyclohexa-1,3-dione so formed precipitated out of the solvent as white solid after the completion of the reaction within 1.5 h. Water was added to the reaction mixture and the white solid was filtered. The solid precipitate was washed with water several times, dried and stored in an airtight bottle.

Bromination of Carbonyl and 1,3-Dicarbonyl Compounds

To a solution of β-keto esters (1 mmol) in CH_2Cl_2 (2 mL) under ice cooling was added D-morvaline (10 mol%). After stirring the reaction mixture for 5 min, brominating reagent **B** (1.1 mmol, 327 mg) was added to the reaction mixture followed by PDC (1 mol%). The reaction was allowed to stir under ice cooling until the completion of the reaction as indicated by thin layer chromatography (TLC). After the completion of the reaction, the reaction mixture was poured into water and extracted with CH_2Cl_2 (2×15 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The solid product so obtained after proper drying contains a mixture of both the α-monobrominated product as well as the brominated reagent in its α-monobrominated form (**C**). Next, the solid product was washed with distilled hexane for three times. The required α-monobromo product dissolved in hexane and was separated from the α-monobrominated reagent which was left behind in its solid form because of its high polarity. The monobromo compound so obtained was further purified through a short column of silica and washed with hexane. The product thus obtained in its pure form after evaporating the hexane, was dried and directly analysed by NMR, mass spectroscopy, GC and elemental analyses. The optical purity of the compound was obtained directly. The compound **C** so obtained in the solid form was further brominated to furnish **B** and reused.

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References

[1] For recent reviews on asymmetric halogenation reactions, see: a) M. Oestreich, *Angew. Chem.* **2005**, *117*, 2376; *Angew. Chem. Int. Ed.* **2005**, *44*, 2324; b) S. France, A. Weatherwax, T. Lectka, *Eur. J .Org. Chem.* **2005**, 475; c) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147.

[2] a) M. B. Smith, J. March, in: *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th edn., John Wiley & Sons, New York, **1992**, pp 775–778; b) N. De Kimpe, R. Verhe, *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, Wiley, New York, **1990**.

[3] G. Thomas, *Medicinal Chemistry: An Introduction*, Wiley, New York, **2000**.

[4] a) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147; b) K. Muniz, *Angew. Chem.* **2001**, *113*, 1701; *Angew. Chem. Int. Ed.* **2001**, *40*, 1653;.

[5] a) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359; b) L. Hintermann, D. Broggini, A. Togni, *Helv. Chim. Acta* **2002**, *85*, 1597; c) R. Frantz, L. Hintermann, M. Perseghini, D. Broggini, A. Togni, *Org. Lett.* **2003**, *5*, 1709; d) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240; e) Y. Hamashima, H. Takono, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, *5*, 3225; f) D. Y. Kim, E. J. Park, *Org. Lett.* **2003**, *5*, 1709; g) J.-A. Ma, D. Cahard, *Tetrahedron* **2004**, *60*, 1007; h) J.-A. Ma, D. Cahard, *J. Fluorine Chem.* **2004**, *125*, 1357; i) N. Shibata, T. Ishimaru, T. Nogai, J. Kohno, T. Toru, *Synlett* **2004**, 1703.

[6] a) N, Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728; b) N. Shibata, E. Suzuki, T. Asahi, Y. Takeuchi, *J. Am. Chem. Soc.* **2001**, *123*, 7001.

[7] a) D. Y. Kim, E. J. Park, *Org. Lett.* **2002**, *4*, 545; b) D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1577.

[8] a) A. E. Taggi, H. Wack, A. M. Hafez, S. France, T. Lectka, *Org. Lett.* **2002**, *4*, 627; b) H. Wack, A. E. Taggi, A. M. Hafez, W. J. Dury, III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531.

[9] G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Angew. Chem.* **2005**, *117*, 6375; *Angew. Chem. Int. Ed.* **2005**, *44*, 6219.

[10] A. M. Hafez, A. E. Taggi, H. Wack, J. Esterbrook, T. Lectka, *Org. Lett.* **2001**, *3*, 2049.

[11] a) S. Bertelsen, N. Halland, S. Bachmann, M. Marigo, A. Braunton, K. A. Jørgensen, *Chem. Commun.* **2005**, 4821; b) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.

[12] Y. Zhang, S. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15308.
[13] L. Hintermann, A. Togni, *Helv. Chim. Acta* **2000**, *83*, 2425.
[14] a) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 325; c) A. Cordova, I. Ibrahem, J. Casas, H. Sunden, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772; d) M. Amedjkouh, *Tetrahedron: Asymmetry* **2005**, *16*, 1411; e) A. Cordova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W. W. Liao, *Chem. Commun.* **2005**, 3586; f) W. Zou, I. Ibrahem, P. Dziedzic, H. Sunden, A. Cordova, *Chem. Commun.* **2005**, 4946; g) I. Ibrahem, W. Zou, M. Engqvist, Y. Xu, A. Cordova, *Chem. Eur. J.* **2005**, *11*, 7024; h) A. Bassan, W. Zou, E. Reyes, F. Himo, A. Cordova, *Angew. Chem.* **2005**, *117*, 7190; *Angew. Chem. Int. Ed.* **2005**, *44*, 7028; i) Y. Xu, A. Cordova, *Chem. Commun.* **2006**, 460; j) Y. Xu, W. Zou, H. Sunden, I. Ibrahem, A. Cordova, *Adv. Synth. Catal.* **2006**, *348*, 418.
[15] A. T. Khan, M. A. Ali, P. Goswami, L. H. Choudhury, *J. Org. Chem.* **2006**, *71*, 8961.
[16] a) G. S. Coumbarides, M. Dingjan, M. J. Eames, N. Weerasooriya, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 179; b) H. Yamamoto, *Lewis Acids in Organic Chemistry*, Wiley-VCH, Weinheim, Germany, **2000**, Chapter 18.
[17] Please see the Supporting Information.

