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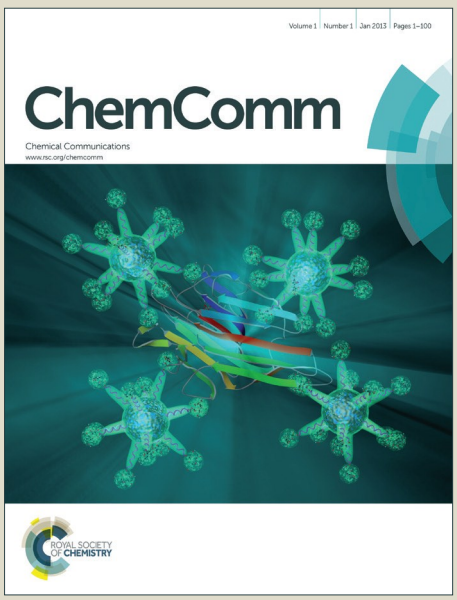

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Construction of All Carbon Quaternary Stereocenter by Organocatalytic Enantioselective α–Functionalization of α-Substituted β-Ketocarbonyls with Electron Deficient Vinylarenes

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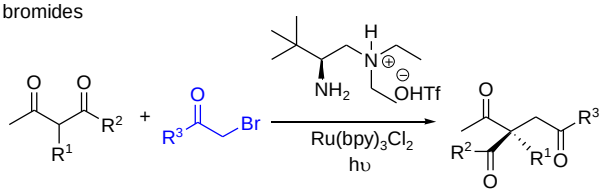
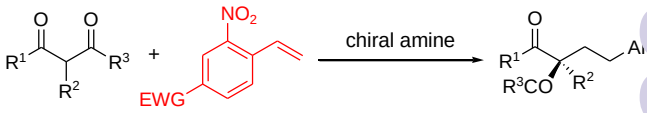
A chiral amine catalyzed enantioselective α-functionalization of α-substituted β-ketocarbonyls with electro-deficient vinylarenes has been developed to construct the dicarbonyl products with formation of a chiral all-carbon quaternary stereocenter. The products can be used for the efficient synthesis of useful but challenging chiral quaternary centered pyrazolones.

The preparation of compounds containing all-carbon quaternary stereocenters with catalytic enantioselective reactions is particularly demanding because their wide distribution in natural products and bioactive substances.[1] However, catalytic enantioselective construction of these centers poses a daunting challenge in spite of the tremendous efforts made in this field.[1] Asymmetric *α*-alkylation of enolizable carbonyl compounds has been proved to be a powerful approach for C-C bond formation. In this context, the alkylation of stereo-defined trisubstituted enolates has been subjected to intensive studies.[2-4] Furthermore, great progress has been made in organocatalytic enantioselective *α*-alkylation of aldehydes in the recent past.[5] However, organocatalytic asymmetric *α*-alkylation of ketones presents a significant difficulty due to the poorer reactivity and the challenge in the discrimination of the prochiral face. Only a handful of examples have been reported.[6] Despite impressive results, the construction of all-carbon quaternary stereocenters remains elusive. Only recently, Luo and co-workers disclosed an elegant solution via a chiral primary amine promoted α-photoalkylation of β-ketocarbonyls with phenacyl bromides (Scheme 1)[7] and List and colleagues described a nice Brønsted acid catalyzed Michael addition of unactivated α-substituted ketones to enones.[8] In this report, we wish to describe a new alternative chiral amine catalyzed enantioselective α-functionalization β-ketocarbonyls with electron-deficient vinylarenes through the direct addition of chiral nucleophilic enamines formed from corresponding substituted β-ketocarbonyls to produce the adducts bearing a all-carbon quaternary stereogenic center (Scheme 1).

Luo: aminocatalytic α-phtotalkylation of β-ketocarbonyls with phenacyl bromides



This work: aminocatalytic α-functionalization of β-ketocarbonyls with electron-defficient arylvinyls



Scheme 1 Organocatalytic enantioselective α-functionalization of substituted β-ketocarbonyls.

Recently, we have initiated a research program o developing new non-classic electrophiles fo organocatalytic enantioselective processes. In these efforts, w have successfully introduced a strategy by incorporatin electron-withdrawing groups (EWGs) such as NO_2, CF_3, an CH_3SO_2 into aromatics and pyridines bearing these EWGs t create new electrophiles[9] and nucleophiles.[10] For example, our more recent study led to the direct chiral amine promote conjugate addition of aldehydes to vinylarenes with high enantioselectivities and the investigation revealed hat introducing an additional electron-withdrawing group on sim 2 or 4-nitrostyrenes enables to generate a highly electrophili vinyl functionality, whose reactivity is comparable to that of β-unsaturated carbonyls.[9] In the further exploration of th chemistry to prepare new synthetically valued chiral building blocks, we turned our attention to a more challenging functionalization of substituted β-ketocarbonyls for the formation of all-carbon quaternary stereocenter.

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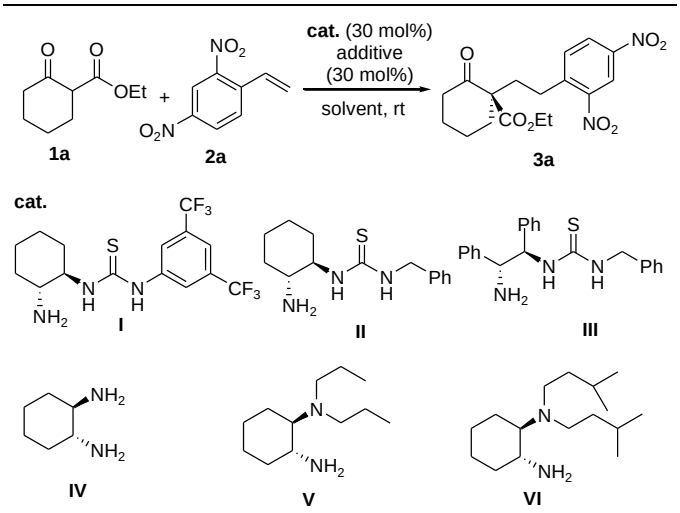
Our initial study commenced with the model reaction between ethyl 2-cyclohexanonecarboxylate **1a** (1.5 mmol) and 2,4-dinitro-1-vinylbenzene **2a** (0.2 mmol) in the presence of chiral primary amine organocatalyst **I** (0.06 mmol) in acetonitrile (Table 1). Although the desired product **3a** was obtained, the reaction proceeded sluggishly with 44% yield and 34% ee after 24 d (entry 1). Screening of primary amine catalysts gave similar results under the same reaction condition (entries 2-5). However, the use of benzoic acid as additive in the presence of amine **V** significantly improved the reaction efficiency (entry 5). Higher yield (70%) and enantioselectivity (78% ee) with dramatically reduced reaction time (5 d) were observed. Encouraged by the outcome, we then further optimized the reaction conditions to improve these parameters.

Table 1 Optimization of reaction conditions[a]



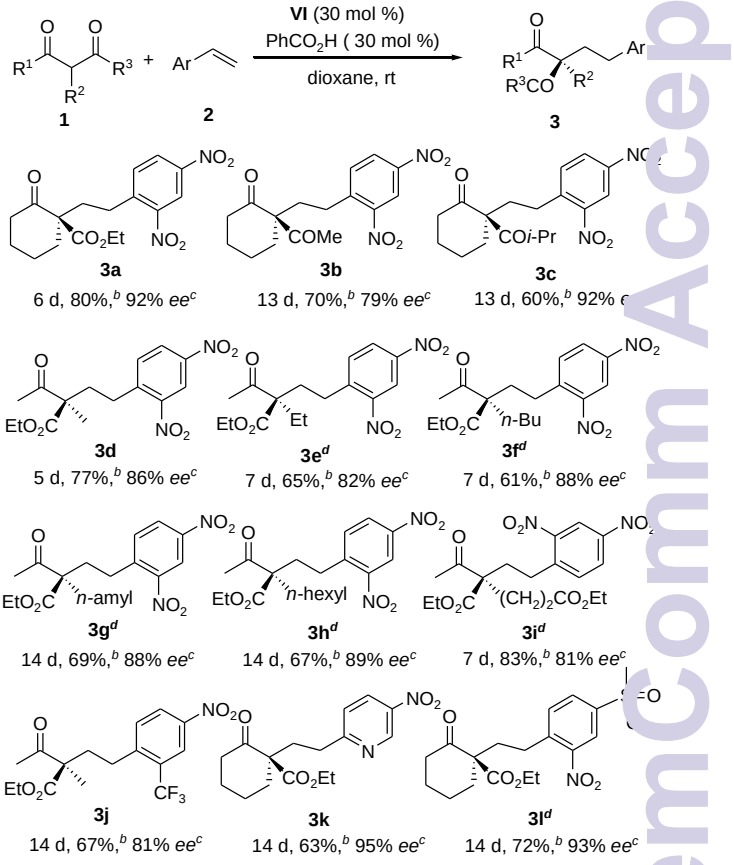
Entry	Cat.	Additive	Solvent	t (d)	Yield (%)[b]	ee (%)[c]
1	**I**	-	CH_3CN	24	44	34
2	**II**	-	CH_3CN	24	45	31
3	**III**	-	CH_3CN	24	33	55
4	**IV**	-	CH_3CN	8	26	51
5	**V**	$PhCO_2H$	CH_3CN	5	70	78
6	**V**	$PhCO_2H$	DCM	5	76	75
7	**V**	$PhCO_2H$	DEM	3	62	80
8	**V**	$PhCO_2H$	DMF	5	48	77
9	**V**	$PhCO_2H$	MeOH	5	84	83
10	**V**	$PhCO_2H$	hexane	7	47	89
11	**V**	$PhCO_2H$	Et_2O	5	59	86
12	**V**	$PhCO_2H$	toluene	8	76	87
13	**V**	$PhCO_2H$	dioxane	6	78	90
14	**VI**	$PhCO_2H$	dioxane	6	80	92

[a] Unless specified, to a solution of **1a** (1.5 mmol) and **2a** (0.2 mmol) in a solvent (600 µL) was added amine catalyst (0.06 mmol) and without or with benzoic acid (0.06 mmol). The resulting solution was stirred at rt for a defined time. The crude reaction mixture was directly purified by column chromatography (petroleum ether/ethyl acetate 8/1 v/v) on silica gel. [b] Isolated yield of product **3a**. [c] Determined by chiral HPLC analysis.

A survey of the reaction solvents revealed that the best performance (84% yield and 83% ee) in methanol (entry 9) was observed than others (entries 6-8 and 10-11). Furthermore, it was gratifyingly found when dioxane was used as the reaction medium, the enantioselectivity could reach to 90% ee in 78% yield (entry 13). Finally, in dioxane and $PhCO_2H$ as co-catalyst, the more bulky primary amine catalyst **VI** gave higher efficiency (entry 14).[11] Therefore, we decided to probe the reaction scope under the conditions of primary amine **VI** with benzoic acid as catalytic system in dioxane.

As shown in Scheme 2, the reactions proceeded smoothly with a wide range of β-ketocarbonyls including β-ketoesters (**3a, 3d-3l**) and β-diketones (**3b** and **3c**) in good to high yields (60-86%) and with high to excellent levels of enantioselectivities (80-95% ee). The processes serve as a general approach to structurally diverse all-carbon quaternary stereocenter contained β-ketocarbonyls. Moreover, both cyclic (**3a-3c** and **3k-3l**) and acyclic (**3d-3j**) β-ketocarbonyls can effectively participate in the process. It seems that the steric hindrance of substituted group on 3-position of diketones was beneficial to enantioselectivity but scarified the reaction yield (**3b** vs **3c**). A similar trend was observed with acyclic ethyl 2-methylacetoacetates (**3d-3i**). At rt, the substrate bearing small

Scheme 2 Substrate scope[a]



[a] Unless specified, see reaction conditions in Table 1, footnote *a* and supporting information. [b] Isolated yield of product. [c] Determined by chiral HPLC analysis. [d] The reaction was run at 50 °C.

sized methyl group was able to proceed in good yield (**3d**). However, slow conversion was observed with longer alkyl chains (**3e-3i**). It was found that elevating the reaction temperature to 50 °C dramatically facilitated the process while maintaining good enantioselectivities (81-89% ee). Structural variation of the arylstyrenes by changing the EWG moieties including CF_3 and CH_3SO_2 at 2-poistion and replacing the phenyl ring with heteroaromatic pyridinyl structure (**3j-3l**) was probed next. The results from the studies showed that the reactions were sensitive to the electronic nature of these substituents. There relatively weaker EWGs required longer reaction time or higher temperature. In cases of 4-nitro-2-(trifluoromethyl)-1-vinylbenzene and 5-nitro-2-vinylpyridine, longer time (14 d) at rt managed to produce adducts **3j** and **3k** with high enatioselectivities in good yields. The reaction between **1a** and 4-(methylsulfonyl)-2-nitro-1-vinylbenzene had to be carried out at 50 °C to give the product **3l** but still afforded the excellent enantioselectivity and good yield.

The absolute configuration of these products with newly formed all-carbon quaternary stereogenic center was determined by single-crystal X-ray diffraction analysis based on compound **3l** (Figure 1).[12]

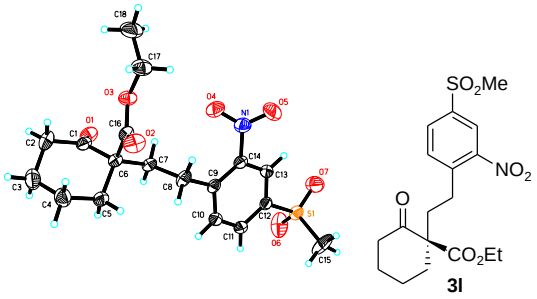
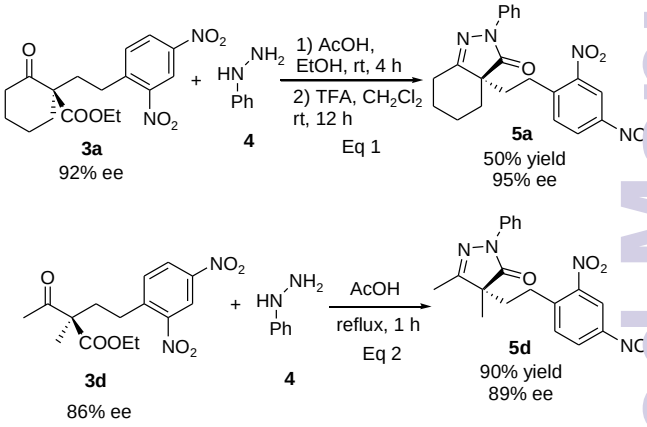


Figure 1 X-Ray crystal structure of compound **3l**.

Pyrazolone derivatives are an important class of heterocyclic compounds which posses a broad spectrum of biological activities in drug discovery.[13] They have been widely used in the study of different kinds of bioactivities such as antitumor,[14] antitubercular,[15] antifungal,[16] and antibacterial activities.[17] Furthermore, pyrazolone derivatives have potent inhibition against protease-resistant isoform of prion protein.[18] In many cases, these molecules contain the important chiral quaternary stereogenic center at C4 position. However, preparation of the chiral pyrazolones is very limited.[19] Herein, we report a new method for the synthesis of the challenging chiral structures by employment of the chiral products from the newly developed process.

The typical method of synthesis of pyrazolones is from the condensation of β-ketoesters and hydrazines under acidic conditions. These chiral β-ketocarbonyl adducts are perfectly adoptable for the reaction as demonstrated in the following transformations using representative cyclic diketone **3a** and acyclic β-ketoester **3d** as examples (Scheme 3). When (*R*)-ethyl 1-(2,4-dinitrophenethyl)-2-oxocyclohexanecarboxylate **3a** treated with phenylhydrazine in acetic acid only led to the formation of an imine intermediate without subsequent cyclization. However, the use of stronger acid (TFA) enabled the cyclization process to proceed to generate the bicyclic pyrazolone **5a** with 50% yield for the two steps and excellent enantioselectivity (Eq 1). Similarly, a solution of (*R*)-ethyl 2-acetyl-4-(2,4-dinitrophenyl)-2-methylbutanoate **3d** and phenylhydrazine **4** in acetic acid was heated to reflux for 1 h to smoothly afford chiral pyrazolone derivative **5d** with 90% yield and 90% ee in a 'one-pot' operation without requiring the employment of stronger TFA (Eq 2).



Scheme 3 Synthesis of chiral pyrazolone derivatives.

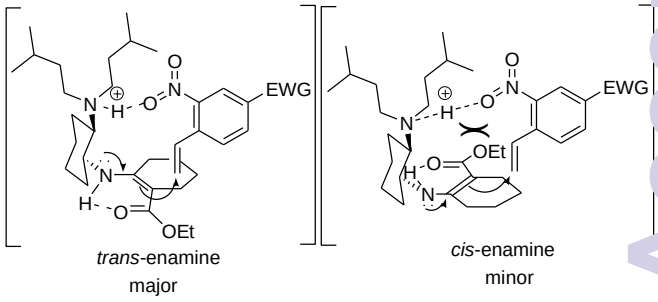


Figure 2 The proposed reaction transition states.

Proposed transition states are provided to rationalize the observed chemical configurations (Figure 2). The chiral primary amine catalyst dictates the formation of more stable *trans*-enamine, which then directs the attack of the C=C bond of the vinyl moiety via the six-membered ring hydrogen-bonding network[7] involved the proton, the basic tertiary amine and the oxygen of nitro group of vinylarene to give the observed (*R*) products. In the 2-vinylpyridine case, the "N" atom instead of "NO_2" moiety interacts the nucleophilic malonate via a similar H-bonding network with the catalyst. Furthermore, the higher steric demand by the catalyst side chain enhances enantioselectivity. The acid additive $PhCO_2H$ plays a critical role in the reaction. It helps to promote the formation of enamine and provide the formation of hydrogen-bonding interaction to improve the reaction yields and ee value.

In conclusion, we have developed a novel organocatalytic enantioselective α-functionalization of α-substituted

ketocarbonyls with our newly developed electron-deficient vinylarenes as non-classic Michael acceptors through a direct conjugate addition. This study represents the first example of the use of these acceptors in the construction of all-carbon quaternary stereogenic center. A wide range of α-substituted β-ketocarbonyls can be tolerated for the process with good to high yields and enantioselectivities (80-95% ee). As demonstrated, the products can be conveniently converted to synthetically and biologically valued but challenging chiral quaternary centered pyrazolones. Further exploration and application of this strategy in the synthesis of biologically relevant molecules are being pursued in our laboratories.

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