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FULL PAPER

Double Activation Catalysis for α′-Alkylidene Cyclic Enones with Chiral Amines and Thiols

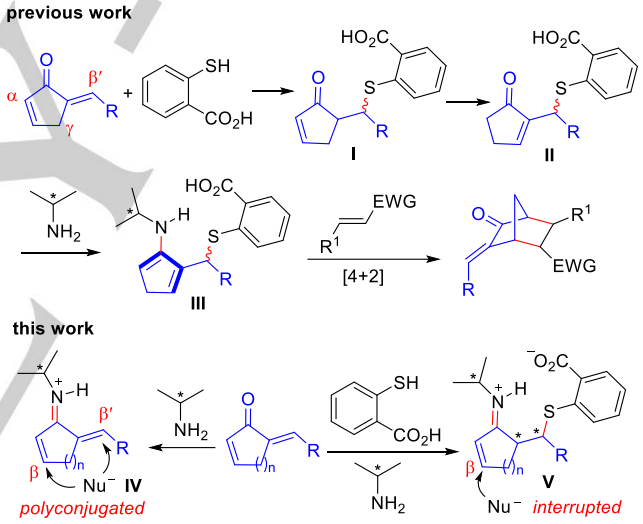
Zhou-Xiang Wang,[a] Zhi Zhou,[a] Wei Xiao,[a] Qin Ouyang,[b] Wei Du,[a] and Ying-Chun Chen*[a,b]

Dedication ((optional))

Abstract: Cooperative catalysis has contributed greatly to the progress of asymmetric synthesis. Nevertheless, the double activation catalysis has been less explored, especially in a covalently tethered pattern. Here we present a double activation strategy for α′-alkylidene cyclic enone substrates with a chiral primary amine and 2-mercaptobenzoic acid, through regio- and chemoselective additions to generate the complex interrupted iminium ion species. Significantly enhanced reactivity and enantioselectivity have been observed in the β-regioselective Michael addition and Friedel–Crafts alkylation reactions with malononitriles and indoles, respectively, producing a spectrum of chiral cyclic adducts with an *exo*-alkylidene group. Moreover, high resolution mass spectroscopy study has finely detected a few key covalently tethered intermediates among substrates and two catalysts, which is helpful for elucidating the catalytic mechanism.

Introduction

Cooperative catalysis is termed that two or more catalysts activate one or two substrates concertedly, which has been widely applied in asymmetric synthesis over the past years.[1] In general, cooperative catalysis can be classified as synergistic catalysis, cascade catalysis, and double activation catalysis. In the case of synergistic catalysis, two substrates are activated by different catalysts simultaneously through separate catalytic cycles to furnish a single chemical transformation.[2] In cascade (tandem/relay) catalysis, the first catalyst decreases the energy barrier of substrates to produce the intermediates, which are further accelerated by the second catalyst.[3] While the strategy of synergistic catalysis has attracted extensive attention and been well exploited as well as cascade catalysis, double activation catalysis,[4] in which either the nucleophile or the electrophile is activated by two catalysts, has been barely explored in asymmetric catalysis. An early example of asymmetric allylation of aldehydes through Pd and amine activation was reported by List, while the enantiocontrol was induced by a counteranion from a chiral phosphoric acid.[5] Importantly, in 2010, the Jacobsen group developed an asymmetric Povarov reaction through a network of noncovalent interactions between imines and a Brønsted acid promoted by a chiral urea.[6] In contrast, there are fewer double activation catalysis instances involving covalent interactions. Shi[7] and Miller[8] independently investigated asymmetric Morita–Baylis– Hillman reaction via a double HOMO-raising activation strategy; however, moderate enantioselectivity was generally obtained. Therefore, the development of new successful covalent double activation catalysis requires thoughtful design and insightful mechanism elucidation.



Scheme 1. Different double activation modes of α′-alkylidene cyclic enones via cooperative amine/thiol catalysis.

Recently, we disclosed that 2-mercaptobenzoic acid could regioselectively add to an α′-alkylidene 2-cyclopentenone, and the resulting intermediate **I** could isomerize to intermediate **II**. Subsequently, a HOMO-raised dienamine species **III** could be generated with a chiral amine catalyst, and underwent an α,γ-regioselective [4+2] cycloaddition reaction with an activated alkene to deliver a bridged product (Scheme 1).[9] Therefore, the cooperative catalysis of thiols[10] and primary amines[11] led to an unusual reaction pathway with α′-alkylidene 2-cyclopentenone substrates. We speculated that the double activation of such dienones with amine and thiol catalysts would have other potential to expand their applications. It could be envisioned that the iminium ion **IV** between a cyclic dienone and an amine might have a relatively low reactivity toward a nucleophile because of the polyconjugated system; in contrast, β′-regioselective sulphur

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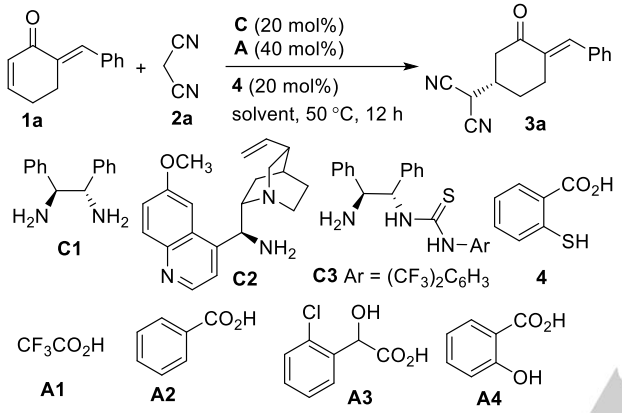
addition of 2-mercaptobenzoic acid to an α′-alkylidene cyclic enone might produce an interrupted iminium ion **V** after reaction with a chiral amine, thus a more effective β-regioselective Michael addition would be furnished accordingly. In addition, the stereogenically tethered sulphide moiety might increase the steric effect, leading to further enhanced enantioselectivity in the asymmetric addition step.

Results and Discussion

Table 1. Screening conditions of asymmetric Michael addition of malononitrile **2a** to 2,2′-dienone **1a**.[a]

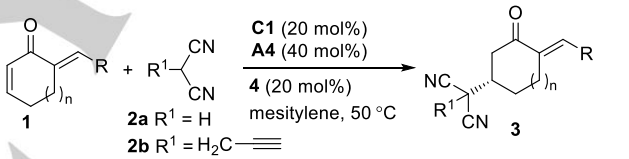


Entry	C	A	Solvent	Yield (%)[b]	*ee* (%)[c]
1[d]	**C1**	**A1**	toluene	trace	/
2[d]	**C1**	**A2**	toluene	45	15
3[d]	**C1**	**A3**	toluene	24	88
4	**C1**	**A2**	toluene	82	91
5	**C1**	**A3**	toluene	80	94
6	**C2**	**A3**	toluene	74	95
7	**C3**	**A3**	toluene	40	94
8	**C1**	**A4**	toluene	82	95
9	**C1**	**A4**	DCE	80	94
10	**C1**	**A4**	*o*-xylene	80	98
11[e]	**C1**	**A4**	mesitylene	85 (86)	98 (97)
12[f]	**C1**	**A4**	mesitylene	85	94

[a] Unless noted otherwise, reactions were performed with 2,2′-dienone **1a** (0.05 mmol), malononitrile **2a** (0.075 mmol), catalyst **C** (20 mol%), acid **A** (40 mol%) and thiol **4** (20 mol%)in solvent (0.5 mL) at 50 °C for 12 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] In the absence of thiol **4**. [e] Data in parentheses were obtained at 5.5 mmol scale. [f] With **C1** (5 mol%), acid **A** (10 mol%) and thiol **4** (20 mol%) for 96 h. DCE = 1,2-dichloroethane.

As the asymmetric Michael additions of malononitrile to α,β-unsaturated ketones, including simple cyclic enones, have been reported previously via aminocatalysis, we initially explored the reaction of α′-benzylidene 2-cyclohexenone[13] **1a** and malononitrile **2a** catalyzed by amine **C1** and trifluoroacetic acid **A1** in toluene. Only trace amounts of product could be detected at 50 °C after 12 h (Table 1, entry 1). A moderate conversion was observed when benzoic acid **A2** was used, but the enantioselectivity for the β-regioselective adduct **3a** was very poor (Table 1, entry 2). A high *ee* value was obtained with a racemic acid **A3**, albeit in a low yield (Table 1, entry 3). In sharp contrast, both yield and enantiocontrol were significantly improved when 2-mercaptobenzoic acid **4** (20 mol%) was added, indicating that the cooperative catalysis of a thiol was crucial for the current reaction (Table 1, entries 4 and 5). It should be noted that the β′-regioselective product was not detected in the above reactions. Moreover, the same enantioselectivity was achieved by using amine **C2** or **C3** in combination with acid **A3**, albeit with lower yields (Table 1, entries 6 and 7). Slightly better data were afforded catalyzed by amine **C1**, thiol **4** and salicylic acid **A4** (Table 1, entry 8). Further solvent screenings (Table 1, entries 9–11) verified that an excellent *ee* value with a high yield was gained in mesitylene, even at a gram scale (Table 1, entry 11). Similar results could be obtained by reducing the loadings of amine **C1**, while a longer time was required (Table 1, entry 12).

Table 2. Reaction scope of malononitriles **2** and 2,2′-dienones **1**.[a]



Entry	R	N	*t* (h)	Yield (%)[b]	*ee* (%)[c]
1	Ph	1	18	**3a**, 85	98
2	3-ClC$_6$H$_4$	1	18	**3b**, 91	97
3	2-BrC$_6$H$_4$	1	18	**3c**, 83	>99
4	4-BrC$_6$H$_4$	1	18	**3d**, 73	98
5	4-MeC$_6$H$_4$	1	18	**3e**, 84	90
6	2-MeOC$_6$H$_4$	1	18	**3f**, 78	98
7	3-MeOC$_6$H$_4$	1	18	**3g**, 93	99
8	2-Naphthyl	1	18	**3h**, 70	>99
9	2-Thienyl	1	18	**3i**, 83	96
10[e]	*n*-Pentyl	1	48	**3j**, 50	93
11	Phenylethyl	1	48	**3k**, 72	90
12[e]	*c*-Hexyl	1	18	**3l**, 53	96
13	Ph	0	48	**3m**, 46	90
14	4-BrC$_6$H$_4$	0	96	**3n**, 58	90
15	4-MeOC$_6$H$_4$	0	96	**3o**, 35	86

16[e]	*i*-Propyl	0	48	**3p**, 40	81
17[f]	Ph	1	20	**3q**, 88	93
18[f]	Ph	0	48	**3r**, 81	81

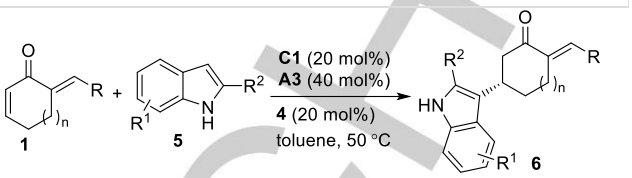
[a] Unless noted otherwise, reactions were performed with 2,2′-dienone **1** (0.1 mmol), malononitrile **2a** (0.15 mmol), catalyst **C1** (20 mol%), acid **A4** (40 mol%) and thiol **4** (20 mol%) in mesitylene (1.0 mL) at 50 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of **3a** was determined by X-ray analysis.[15] The other products were assigned by analogy. [e] With **1** (0.15 mmol) and **2a** (0.1 mmol). [f] **2b** was used at 35 °C.

Consequently, we explored the generality of asymmetric Michael additions of malononitriles **2** to a diverse range of α′-alkylidene cyclic enones **1** under the double activation of amine **C1** and thiol **4** in the presence of acid **A4**. The results are summarized in Table 2. In general, 2,2′-dienones with a β′-aryl or a β′-heteroaryl group could be well tolerated, and moderate to high yields with excellent enantioselectivity were obtained smoothly (Table 2, entries 1–9). 2,2′-dienones with a linear or a branched β′-alkyl group exhibited lower reactivity, but high enantiocontrol was retained (Table 2, entries 10–12). On the other hand, it was found that only fair to moderate conversions were attained when a few α′-alkylidene cyclopentenones were utilized probably due to the more crowded structures, and the enantioselectivity was also slightly decreased (Table 2, entries 13–16).[14] A propargylmalononitrile **2b** showed higher reactivity, and good results were obtained (Table 2, entries 17 and 18).[12b]

The successful double activation strategy of amine and thiol for β′-alkylidene cyclic enones promoted us to investigate other β-functionalization reactions. As illustrated in Table 3, the Friedel–Crafts (FC) reaction of indole **5a** ($R^1 = R^2 = H$) with α′-benzylidene 2-cyclohexenone **1a** proceeded sluggishly under the catalysis of amine **C1** and acid **A3** in toluene at 50 °C, and a moderate yield with a good *ee* value for product **6a** was obtained after 96 h (Table 3, entry 1).[16] As expected, the reactivity was dramatically enhanced by adding catalytic amounts of 2-mercaptobenzoic acid **4**, giving **6a** in 94% yield after 72 h with outstanding enantioselectivity (Table 3, entry 2).[17] Subsequently, we explored the reaction scope and limitations of the new FC reaction. In general, moderate to high yields and enantioselectivity were obtained for cyclohexenones **1** with diverse α′-alkylidene groups in reactions with indole **5a** (Table 3, entries 2–8). In addition, indoles with either a 2-methyl or a 2-phenyl group showed high reactivity in reactions with dienone **1a**, delivering products **6h** and **6i** with good enantioselectivity, respectively (Table 3, entries 9 and 10). Although lower reactivity was observed for indoles with a substituent on the aryl ring, the enantiocontrol was satisfactory (Table 3, entries 11–13). Moreover, we tested the reactions between indole **5a** and a few α′-alkylidene cyclopentenones, and moderate enantioselectivity was generally afforded (Table 3, entries 14–18).[14]

We proposed a plausible catalytic cycle to gain more insight into the catalytic mechanism. As outlined in Scheme 3, thiol **4** may reversibly and β′-regioselectively add to 2,2′-dienone **1a**, giving

Table 3. Friedel–Crafts Reaction scope of alkylations of indoles **5** with 2,2′-dienones **1**.[a]



Entry	R	R^1, R^2	n	*t* (h)	Yield (%)[b]	*ee* (%)[c]
1[d]	Ph	H, H	1	96	**6a**, 60	85
2	Ph	H, H	1	72	**6a**, 94	94
3	4-ClC_6H_4	H, H	1	48	**6b**, 91	95
4	3-BrC_6H_4	H, H	1	48	**6c**, 91	84
5	4-MeC_6H_4	H, H	1	48	**6d**, 89	83
6	2-$MeOC_6H_4$	H, H	1	48	**6e**, 68	84
7[e]	*n*-Butyl	H, H	1	72	**6f**, 60	91
8[e]	*c*-Hexyl	H, H	1	48	**6g**, 52	88
9[f]	Ph	CH_3, H	1	24	**6h**, 92	80
10[f]	Ph	Ph, H	1	24	**6i**, 93	86
11	Ph	H, 6-Br	1	72	**6j**, 55	90
12	Ph	H,6-CH_3	1	72	**6k**, 51	94
13	Ph	H, 5-MeO	1	48	**6l**, 57	88
14	Ph	H, H	0	48	**6m**, 80	85
15	4-BrC_6H_4	H, H	0	48	**6n**, 82	79
16	4-$MeOC_6H_4$	H, H	0	48	**6o**, 66	77
17	3-Furyl	H, H	0	48	**6p**, 98	74
18	*i*-Propyl	H, H	0	96	**6q**, 32	73

[a] Unless noted otherwise, reactions were performed with 2,2′-dienone **1** (0.1 mmol), indole **5** (0.2 mmol), catalyst **C1** (20 mol%), acid **A3** (40 mol%) and thiol **4** (20 mol%) in toluene (1.0 mL) at 50 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] In the absence of thiol **4**. [e] With 2,2′-dienone **1** (0.12mmol) and indole **5** (0.1 mmol) at 35 ℃. [f] At 35 ℃.

the intermediate **I**. Subsequently, chiral amine **C1** may react with a more stereogenically matched enone **I** to afford the key iminium ion **V**, which can be attacked by malononitrile **2a** from *Si*-face. Subsequently, elimination of thiol **4** from adduct **VI** occurs, delivering the imine intermediate **VII**, which can be finally hydrolyzed to produce adduct **3a** and amine **C1**. Pleasingly, the key intermediates **I**, **V**, **VI** and **VII** have been successfully detected by high resolution mass spectroscopy (HRMS) study, verifying that the current reaction would proceed in a covalent double activation catalytic pathway.[14]

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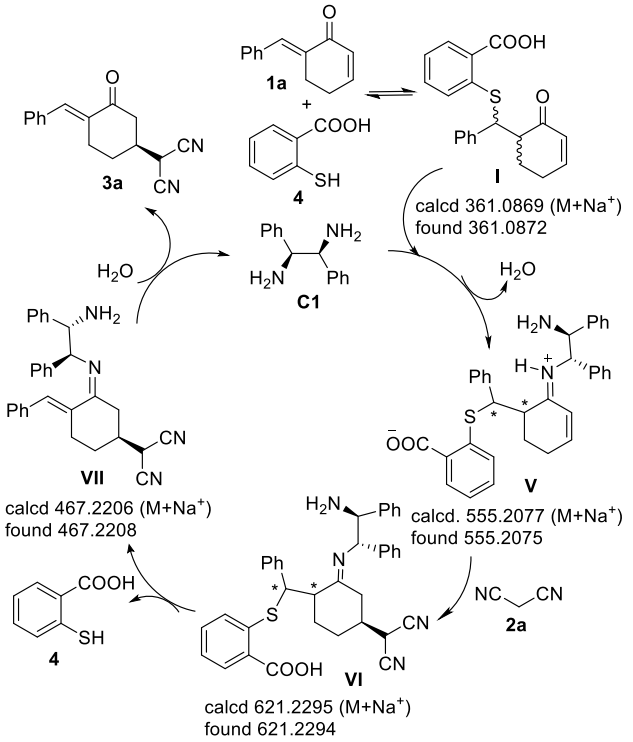

Scheme 2.HRMS study of the key intermediates in the Michael addition cycle via double activation catalysis.

Moreover, preliminary density functional theory (DFT) computational calculations were performed to clarify the catalytic reactivity of double activation. As showed in Figure 1, owing to the interruption of thiol addition, the carbon at β-site (–0.024) in the stereogenically optimized intermediate **V** has a more positive natural population analysis (NPA) charge than that at β-site (–0.045) in the polyconjugated iminium ion **IV**, suggesting it should be easier to be attacked by a nucleophile.[16]

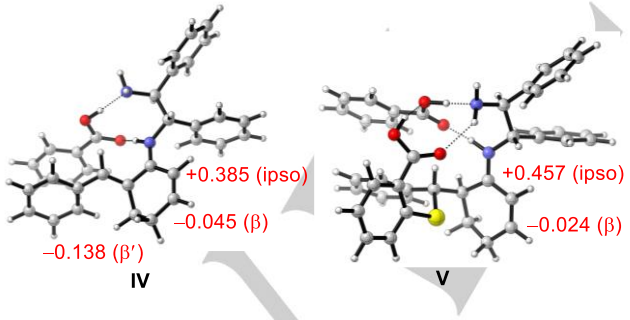

Figure 1. The geometries and NPA charges of iminium ions **IV** and **V**.

Conclusions

In conclusion, we have disclosed that a chiral primary amine and 2-mercaptobenzoic acid can covalently react with α′-alkylidene cyclic enones regio- and chemoselectively, leading to the formation of the interrupted iminium ion intermediates. Significantly enhanced reactivity and enantioselectivity have been observed in the subsequent β-regioselective Michael additions with malononitriles and Friedel–Crafts alkylations with indoles, respectively, furnishing a spectrum of chiral cyclic products with an *exo*-alkylidene group in moderate to excellent enantioselectivity. Moreover, a few key species via covalent double activation catalysis have been successfully elucidated based on high resolution mass spectroscopy analysis. Currently, the development of more asymmetric reactions with multifunctional dienone substrates via amine and thiol cooperative catalysis is under way.

Experimental Section

General

For the synthesis of starting materials, full characterization data, NMR spectra, and HPLC traces, see the Supporting Information.The research data underpinning this publication can be accessed at DOI:

General procedure for asymmetric Michael additions of malononitriles to 2,2′-dienones

2,2′-Dienone **1** (0.1 mmol), malononitrile **2** (0.15 mmol), catalyst **C1** (20 mol%), acid **A4** (40 mol%) and 2-mercaptobenzoic acid **4** (20 mol%) were added into a vial equipped with a magnetic stir bar. Mesitylene (1.0 mL) was added. The mixture was stirred at the indicating temperature and monitored by TLC. After completion, the resulting crude residue was purified by column chromatography on silica gel eluting with (EtOAc/petroleum ether = 1/30–1/8) to afford the product **3**.
Some *Z*-configured isomers will be generated from the previously formed *E*-products **3** upon standing. ^{1}H NMR, ^{13}C NMR and HPLC data refer to the products **3** with an *E*-configuration.

(*S*,*E*)-2-(4-Benzylidene-3-oxocyclohexyl)malononitrile (3a)

Obtained as a yellow solid in 85% yield after flash chromatography and the enantiomeric excess was determined to be 98% by HPLC analysis on chiralpak ID column (40% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, t_{major} = 11.21 min, t_{minor} = 8.56 min; $[\alpha]_D^{20}$ = +208.4 (*c* = 1.24 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.64 (s, 1H), 7.46–7.35 (m, 5H), 3.77 (d, *J* = 5.6 Hz, 1H), 3.24 (d, *J* = 16.4 H z, 1H), 3.00–2.90 (m, 1H), 2.81–2.73 (m, 1H), 2.73–2.66 (m, 1H), 2.64 (d, *J* = 8.6 Hz, 1H), 2.47 (dd, *J* = 16.8, 12.4 Hz, 1H), 2.30–2.21 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* (ppm) 196.0, 138.5, 134.7, 132.7, 130.4, 129.4, 128.6, 111.0, 110.8, 42.6, 36.7, 28.5, 26.9, 26.6; ESI-HRMS: calcd. for $C_{16}H_{14}N_2O$+Na$^+$ 273.0998, found 273.0999.

General procedure for asymmetric Friedel–Crafts alkylations of indoles with 2,2′-dienones

2,2′-Dienone **1** (0.1 mmol), indole **5** (0.2 mmol), catalyst **C1** (20 mol%), acid **A3** (40 mol%) and 2-mercaptobenzoic acid **4** (20 mol%) were added into a vial equipped with a magnetic stir bar. Toluene (1.0 mL) was added. The mixture was stirred at the indicating temperature and monitored by TLC. After completion, the resulting crude residue was purified by column chromatography on silica gel eluting with (EtOAc/petroleum ether = 1:15) to afford the product **6**.

Some *Z*-configured isomers will be generated from the previously formed *E*-products **6** upon standing. ^{1}H NMR, ^{13}C NMR and HPLC data refer to the products **6** with an *E*-configuration.

(*S*,*E*)-2-Benzylidene- 5-(*1H*-indol-3-yl)cyclohexan-1-one (6a)

Obtained as a yellow solid in 94% yield after flash chromatography and the enantiomeric excess was determined to be 94% by HPLC analysis on Chiralcel OD-H column (40% 2-propanol/*n*-hexane, 1 mL/min), UV 254 nm, t_{major} = 6.89 min, t_{minor} = 12.33 min; $[\alpha]_D^{20}$ = +123.4 (*c* = 0.46 in $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.05 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.47–7.29 (m, 6H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 3.64–3.57 (m, 1H), 3.06 (dd, *J* = 17.4, 3.6 Hz, 1H), 2.97 (dt, *J* = 14.8, 4.8 Hz, 1H), 2.89–2.85 (m, 1H), 2.79 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.38–2.25 (m, 1H), 2.07–1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 201.7, 136.6, 136.0, 135.9, 135.6, 130.5, 128.7, 128.4, 126.3, 122.3, 120.4, 119.5, 119.4, 119.1, 111.4, 46.6, 32.3, 30.3, 27.5; ESI-HRMS: calcd. for $C_{21}H_{19}NO+Na^+$ 324.1359, found 324.1363.

Acknowledgements

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Keywords: double activation catalysis • aminocatalysis • thiol catalysis • Michael addition • Friedel–Crafts alkylation

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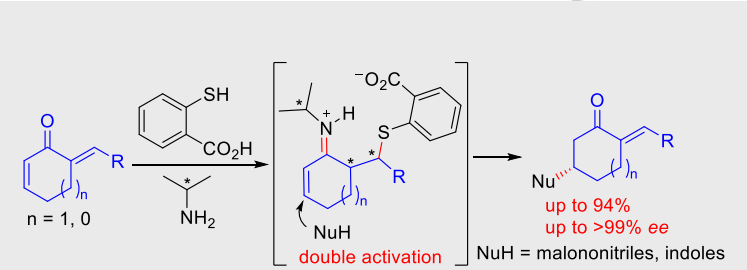

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Double Activation Catalysis for α′-Alkylidene Cyclic Enones with Chiral Amines and Thiols

Double activation: Complex iminium ion species are generated among α′-alkylidene cyclic enones, a chiral primary amine and 2-mercaptobenzoic acid regio- and chemoselectively, leading to significantly enhanced reactivity and enantioselectivity in the subsequent β-regioselective Michael additions with malononitriles and Friedel–Crafts alkylations with indoles.