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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9353–9357

Double catalytic enantioselective Michael addition reactions of tertiary nucleophile precursors—tertiary/quaternary and quaternary/quaternary carbon–carbon bond formations

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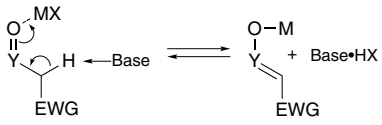
Received 19 September 2006; revised 10 October 2006; accepted 13 October 2006
Available online 9 November 2006

Abstract—Enantioselective Michael addition reactions of tertiary nucleophile precursors, such as substituted malononitriles and cyclic 1,3-diketones, can be successfully activated by the metal complexes derived from *R*,*R*-DBFOX/Ph chiral ligand and cationic metal salts. With this method, the enantioselective tertiary/quaternary and quaternary/quaternary carbon–carbon bond formations can be achieved. Use of alcohol solvents is essential for the success, and α,β-unsaturated amides of 3,5-dimethylpyrazole are much better acceptors than those of 2-oxazolidinone.

We have recently developed some new catalytic activation methods of nucleophile precursors and these have been successfully applied to the catalyzed enantioselective Michael addition reactions. When nucleophile precursors coordinate to a Lewis acid catalyst, the hydrogen α to the electron-withdrawing group becomes more acidic so that the α-hydrogen may be deprotonated with external amines to generate the corresponding metal enolates as reactive nucleophilic intermediates (Eq. 1).[1] Metal carboxylates are also utilized, instead of the combined use of Lewis acids and amines, to generate the metal enolates with the concurrent liberation of the corresponding carboxylic acids (Eq. 2).[2] Since the carboxylic acids thus formed work as quenching agents toward the resulting metal enolates, the process of catalytic metal enolization with metal carboxylates becomes reversible. The metal enolates thus generated have been successfully applied to the catalytic enantioselective reactions under absolutely neutral conditions.

On the other hand, cationic metal salts having noncoordinating counteranions should work more effectively as stronger Lewis acids to activate nucleophile precursors



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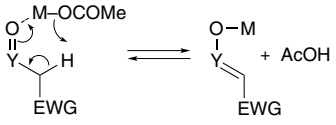
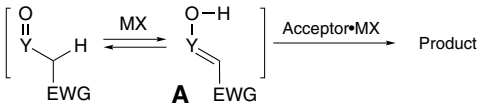


(2)



(3)

making the α-hydrogen more acidic. However, the catalytic generation of metal enolates is difficult only by the action of cationic Lewis acid catalysts, because the protonic acids simultaneously formed are strong enough to protonate the resulting metal enolates. As a result, the equilibration should move to the side of the starting precursors.[3] Even so, we expected that both acceptors and nucleophile precursors would be activated by action of a single Lewis acid MX if appropriate nucleophile precursors and reaction solvents are combined. Our

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0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.10.089

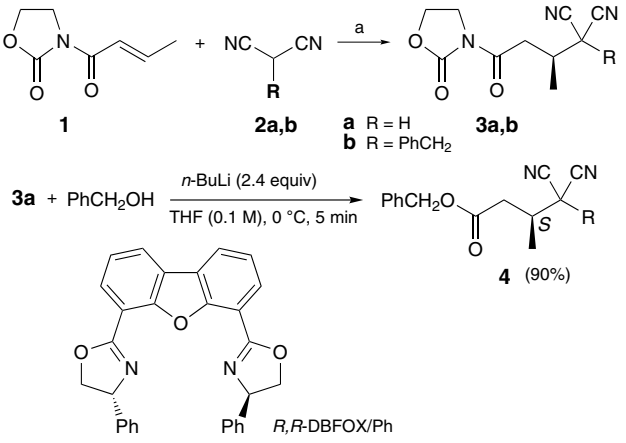
anticipation is that nucleophile precursors are catalyzed to isomerize into enols **A**, and acceptors become more electrophilic in the presence of strong Lewis acid catalysts (Eq. 3). This double catalytic activation provides a great synthetic advantage such that enols **A** can exceed in concentration the catalytic amount of MX. On the contrary, the previous two methods shown in Eqs. 1 and 2 have an unfavored limitation that the metal enolates generated never exceed the amount of catalyst MX. Of course, right selection of nucleophile precursors as well as reaction solvents is critical.

We would like to present, in the present letter, the enantioselective Michael addition reactions of substituted malononitriles and cyclic 1,3-diketones, catalyzed by the metal complexes derived from *R*,*R*-DBFOX/Ph chiral ligand and cationic metal salts.[4] Tertiary nucleophilic precursors can be successfully activated by this method to allow the enantioselective production of adducts through tertiary/quaternary and quaternary/quaternary carbon–carbon bond formations.

The reaction of 3-crotonoyl-2-oxazolidinone (**1**) with malononitrile (**2a**) in the presence of a catalytic amount of the *R*,*R*-DBFOX/Ph complex of nickel(II) perchlorate hexahydrate (10 mol %) at room temperature was too slow taking three days when either dichloromethane or THF was chosen. The corresponding Michael adduct **3a** was obtained only in low yields and enantioselectivities, respectively (entries 1 and 2 of Table 1). However, the same reaction was much more accelerated in methanol/THF 1:1 mixture; the reaction was complete in 7 h at room temperature to give **3a** in 81% yield with the enantioselectivity of 84% ee (entry 3).[5] In the latter case, THF was employed to improve the solubility of the *R*,*R*-DBFOX/Ph–Ni(II) complex catalyst, and no trace of the 2:1 adduct was detected.[6] Thus, the use of polar alcohol solvent was highly effective for the enhancement of the reaction rate as well as the improvement of enantioselectivity. The adduct **3a** was transformed into the known (*S*)-ester **4** on treatment with lithium benzyloxide at 0 °C for a short time period, confirming the absolute configuration of **3a** to be *S*-enantiomer.[1b]

With the tertiary nucleophile precursor **2b** having an additional substituent, the reaction of **1** in dichloromethane or THF was again very slow (entries 4 and 5). On the other hand, the same reaction was complete in 9 h at room temperature in methanol/THF 1:1 mixture (entry 6). The adduct **3b**, produced through the tertiary/quaternary carbon–carbon bond formation, was obtained in a quantitative yield with the enantioselectivity of 76% ee. Thus, the Michael addition reaction between **1** and **2b** should be better carried out also in alcohol solvents. Other alcohol solvents such as ethanol and isopropyl alcohol were only a little less effective than methanol, but adduct **3b** was produced almost quantitatively after the reaction time of 24 h

Table 1. Michael addition reactions catalyzed by cationic metal complexes in several reaction solvents[a]



Entry	2	Solvent	Time (h)	3	Yield (%)	ee (%)
1	**2a**	CH_2Cl_2	72	**3a**	40	5
2		THF	72		20	21
3		MeOH/THF (1:1)	7		81	84
4	**2b**	CH_2Cl_2	72	**3b**	69	53
5		THF	72		71	76
6		MeOH/THF (1:1)	9		Quant	76
7		EtOH/THF (1:1)	24		97	80
8		EtOH/THF (1:1)[b]	24		83	83
9		EtOH/THF (1:1)[c]	24		94	82
10		*i*-PrOH/THF (1:2)	24		Quant	77
11		*t*-BuOH/THF (1:2)	24		65	70

[a] *R*,*R*-DBFOX/Ph + $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol % each), rt. Additive (2 mol %).
[b] AcOH.
[c] Trifluoroacetic acid.

(entries 7 and 10); the reaction in *t*-butyl alcohol gave **3b** in 65% yield (entry 11). Use of catalytic amounts (2 mol %) of acidic additives such as acetic acid and trifluoroacetic acid provided little better enantioselectivities of 82–83% ees (entries 8 and 9). The absolute configurations of **3a**–**c** were tentatively assigned to be *S*-enantiomers based on the similarity of chirality with that of **3a**.

Pyrazole acceptor **5** was found to be much more reactive than 2-oxazolidinone substrate **1** and a higher enantioselectivity was observed in the reaction of **5** (Table 2). Thus, methylmalononitrile (**2c**) reacted with 1-crotonoyl-3,5-dimethylpyrazole (**5**) in 8 h at room temperature even in *t*-BuOH/THF 1:1 mixture in the presence of a catalytic amount of the *R*,*R*-DBFOX/Ph complex of nickel(II) perchlorate hexahydrate (10 mol %), to give the adduct **6c** in 90% yield with the enantioselectivity of 97% ee (entry 1). Alcohols are the best solvents of choice and the reactions are slower in less polar solvents such as THF, dichloromethane, and toluene (entries 2–4). However, in this case lower alcohols such as methanol and ethanol have to be avoided to use since 1-acyl-3,5-dimethylpyrazole **5** undergoes ready alcoholysis at room temperature under the catalyzed conditions to give the corresponding esters. We were fortunate to find that the 1:1 mixture of *t*-BuOH/THF as bulky alcohol could be safely used as the reaction solvent where THF was needed again to improve the solubility of *R*,*R*-DBFOX/Ph complex.

The *R*,*R*-DBFOX/Ph cationic complexes of nickel(II) and cobalt(II) salts were the best catalysts for catalytic activity as well as enantioselectivity (entries 1 and 5). Zinc triflate and magnesium perchlorate were a little less reactive catalysts (entries 6 and 7).

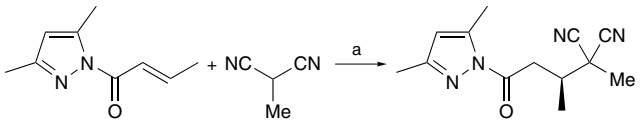
The reaction of 1-crotonoyl-3,5-dimethylpyrazole (**5**) with malononitrile (**2a**) in *t*-BuOH/THF 1:1 mixture was quickly finished in 4 h at room temperature to give a mixture of two products **6a** and **7** in 69 and 14% yields, respectively (entry 1 of Table 3). The adduct **6a**, obtained with the enantioselectivity of 87% ee, was assigned as the *S*-enantiomer by comparison with the authentic sample,[1b] and the side product **7** obtained as a single diastereomer was tentatively assigned as the *S*,*S*-enantiomer of 2:1 adduct between **5** and **2a**. Formation of the 2:1 adduct **7** indicates that the 1:1 adduct **6a** has reacted with another molecule of acceptor **5**, after further enol formation.

Reactions of **5** with tertiary nucleophile precursors **2b**,**c** were also relatively finished fast to give the Michael adducts **6b**,**c** in excellent enantioselectivities through the tertiary carbon–quaternary carbon bond formation (entries 2 and 3). When the β-substituent of pyrazole amide acceptors **8**, **9** is bulkier such as R^1 = isopropyl, R^2 = H and R^1 = phenyl, R^2 = H, the reaction takes a long time period to finish (entries 4 and 5). The ester-substituted acceptor **10** was highly reactive toward methylmalononitrile (**2c**) so that the reaction was complete in 1.5 h to provide excellent yield and exclusive enantioselectivity (entry 6).

Reaction of 1-[(*E*)-3-ethoxycarbonyl-2-butenoyl]-3,5-dimethylpyrazole (**11**) as β,β-disubstituted electrophile with malononitrile (**2a**) took 36 h at room temperature to give the adduct **15a** having a chiral quaternary carbon in 94% yield with the enantioselectivity of 85% ee (entry 7). It is our pleasure that the quaternary carbon–quaternary carbon bond formation was successful in the reactions of **11** with **2b**,**c** to give the corresponding adducts **15b**,**c** having the contiguous chiral quaternary carbon centers, albeit the reaction took two days at room temperature and enantioselectivities were a little lower than 80% ee (entries 8 and 9).

Dimedone (**16a**) as cyclic 1,3-diketone was also activated in an alcohol solvent. Thus, the reaction of **16a** with **5** in *i*-PrOH/THF 1:1 mixture in the presence of acetic anhydride (1 equiv) at room temperature was complete in 29 h to give enol lactone **17** in 78% yield with the enantioselectivity of 94% ee (entry 1 of Table 4).[7] When 1,1,1,3′,3′,3′-hexafluoro-2-propanol (HFIP) was used as acidic alcohol together with THF, the reaction between **5** and **16a** was complete only in 1 h to give **17** in 45% (85% ee), and 3,5-dimethyl-1-[3-(1,1,1,3′,3′,3′-hexafluoro-2-propyloxy)butanoyl]pyrazole (**20**) was also produced as Michael adduct of HFIP to **5** in 51% yield with the enantioselectivity of 69% ee (entry 2). With the

Table 2. Cationic metal salt catalyzed enantioselective Michael addition reactions of pyrazole substrates in several solvents[a]

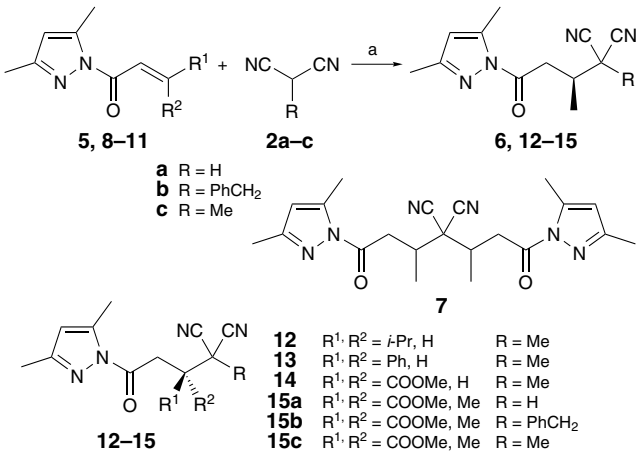


5 **2c** **6c**

Entry	Metal salt	Solvent	Yield (%)	ee (%)
1	$Ni(ClO_4)_2{\cdot}6H_2O$	*t*-BuOH/THF (1:1)	90	97
2	$Ni(ClO_4)_2{\cdot}6H_2O$	THF	67	97
3	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	57	92
4	$Ni(ClO_4)_2{\cdot}6H_2O$	Toluene	45	92
5	$Co(ClO_4)_2{\cdot}6H_2O$	*t*-BuOH/THF (1:1)	94	95
6	$Zn(OTf)_2$	*t*-BuOH/THF (1:1)	73	94
7	$Mg(ClO_4)_2$	*t*-BuOH/THF (1:1)	54	21

[a] *R*,*R*-DBFOX/Ph + metal salt (10 mol % each), rt, 8 h.

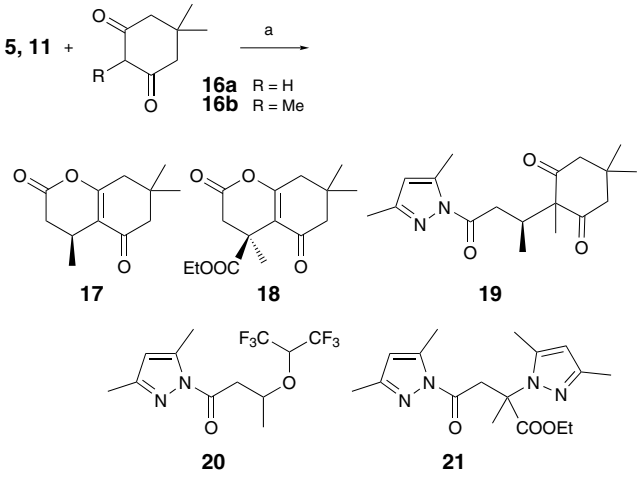
Table 3. Cationic Ni(II) catalyzed enantioselective Michael addition reactions of pyrazole substrates in alcohol media[a]



Entry	Acceptor (R^1, R^2)		Donor	Time (h)	Product	Yield (%)	ee (%)
1	**5**	Me, H	**2a**	4	**6a**	69, 14[b]	87
2			**2b**	12	**6b**	92	95
3			**2c**	8	**6c**	90	97
4	**8**	*i*-Pr, H	**2c**	36	**12**	33	91
5	**9**	Ph, H	**2c**	36	**13**	82	92
6	**10**	COOEt, H	**2c**	1.5	**14**	91	99
7	**11**	COOEt, Me	**2a**	36	**15a**	94	85
8			**2b**	48	**15b**	77	76
9			**2c**	48	**15c**	55	72

[a] *R*,*R*-DBFOX/Ph + $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol % each), *t*-BuOH/THF (1:1), rt.
[b] Yields for **6a** and **7**, respectively.

Table 4. Michael addition reactions of dimedones in alcohol media[a]



Entry	Donor	Acceptor	Solvent	Time (h)	Product	Yield (%)	ee (%)
1	**16a**	**5**	*i*-PrOH/THF (1:1)	29	**17**	78	94
2			HFIP/THF (1:1)	1	**17**	45[b]	85
3		**11**	*t*-BuOH/THF (1:1)	48	**18**	35[c]	59
4	**16b**	**5**	*t*-BuOH/THF (1:1)	48	**19**	42	91

[a] *R*,*R*-DBFOX/Ph + $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol % each), Ac_2O (1 equiv), alcohol/ THF = 1:1 v/v (0.33 M), Ac_2O (1 equiv), rt.
[b] Accompanied by the alcohol adduct **20** in 51% yield (69% ee).
[c] Accompanied by the adduct **21** in 33% yield.

β,β-disubstituted 1-acryloyl-3,5-dimethylpyrazole **11** and dimedone (**16a**), the corresponding enol lactone **18** having two quaternary carbons, one of them as a chiral center, was obtained in 42% yield with 91% ee together with the pyrazole adduct **21**, while the reaction rate was very slow (entry 3). The reaction of **5** with tertiary nucle-

ophile precursor **16b** gave the Michael adduct **19** in a good enantioselectivity of 91% ee, but the yield was rather poor (entry 4).

In conclusion, highly enolizable tertiary nucleophile precursors such as substituted malononitriles and cyclic 1,3-diketones undergo enantioselective Michael addition reactions to the α,β-unsaturated amides derived from 2-oxazolidinones and 3,5-dimethylpyrazole in the presence of the *R*,*R*-DBFOX/Ph complex of cationic nickel(II) or cobalt(II) ion in alcohol solvents. Therein the same chiral catalyst acts effectively to activate both nucleophile precursors and electrophilic acceptors to induce the enantioselective tertiary/quaternary and quaternary/quaternary carbon–carbon bond formations. Use of alcohol solvents is essential for the success, and unsaturated amides of 3,5-dimethylpyrazole are much better acceptors than those of 2-oxazolidinone.

Acknowledgment

S.K. was financially supported for this work by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research (B), 17350049, 2005–2006.

References and notes

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2. Catalytic metal enolization using metal carboxylates: Hasegawa, M.; Ono, F.; Kanemasa, S. unpublished results.
3. Relatively less enolizable nucleophilic precursors such as nitromethane cannot be activated only with cationic metal salts such as $Ni(II)X_2{\cdot}6H_2O$ ($X = ClO_4$ or BF_4), indicating the use of nucleophile precursors with highly acidic α-hydrogen(s) is important in this work.
4. Cationic nickel(II) ion catalyzed Michael addition/enol lactonization reactions of β-keto esters have been achieved in ethyl acetate Evans, D. A.; Thomson, R. J.; Franco, F. *J. Am. Chem. Soc.* **2005**, *127*, 10816–10817.
5. Typical experimental procedure is given for the reaction between 3-crotonoyl-2-oxazolidinone (**1**) with malononitrile (**2a**): To a solution of tetrahydrofuran (THF) and methanol (0.3 mL each) were added nickel(II) acetate tetrahydrate (7.3 mg, 0.02 mmol) and (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyl-2-oxazoline) (*R*,*R*-DBFOX/Ph, 9.2 mg, 0.02 mmol), and the solution was stirred at room temperature for 1 h. The electrophile **1** (31 mg, 0.2 mmol) was added and the stirring was continued for 30 min; the nucleophile precursor **2a** (13.2 mg, 0.2 mmol) was added and the mixture was stirred for 7 h. The reaction was monitored by TLC. The resulting mixture was filtered through a short column ($\phi = 20$ mm), packed with silica gel (height: 30 mm) with hexane–ethyl acetate (1:1 v/v) to give a pure sample of 3-(4,4-dicyano-3-methylbutanoyl)-2-oxazolidinone (**3a**, 36 mg, 81%).
Under nitrogen, to a solution of benzyl alcohol (0.19 mL, 1.80 mmol) in THF (3 mL) was added butyllithium (1.57 M in hexane, 0.92 mL, 1.44 mmol) at −78 °C. The mixture was warmed to 0 °C and then stirred for 15 min. A solution of 3-(4,4-dicyano-3-methylbutanoyl)-2-oxazolidinone (**3a**, 130 mg, 0.6 mmol) in THF (4 mL) was added and stirred for 5 min. The reaction mixture was poured into saturated ammonium chloride (5 mL) and extracted with ethyl acetate (8 mL × 3). The combined organic layers were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The crude residue was filtered through a flash silica gel column chromatography (eluted with hexane–ethyl acetate (4/1 v/v)) to provide analytically pure benzyl ester **4** (145 mg, yield = 88%).
Compound **3a**: Colorless viscous liquid; $[\alpha]_D^{25}$ +20.3 (81% ee, *c* 0.15, $CHCl_3$); IR (neat) $\nu = 3013$, 2982, 2943, 2907, 2887, 2253 (weak, CN), 1776, 1695, 1483, 1456, 1396, 1361, 1321, 1261, 1247, 1224, 1200, 1122, 1110, 1037, 1020, 972, 949, 758, 715, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta = 1.94$ (3H, d, $J = 7.0$ Hz, 3-Me), 2.71–2.77 (1H, m, H-3), 3.11 (1H, dd, $J_{gem} = 18.6$ and $J_{2-3} = 8.5$ Hz, one of H-2), 3.23 (1H, dd, $J_{gem} = 18.6$ and $J_{2-3} = 4.8$ Hz, the other of H-2), 4.02 (2H, t, $J_{4'-5} = 8.2$ Hz, H-4 of the 2-oxazolidinone), 4.38 (1H, d, $J_{4-3} = 5.1$ Hz, H-4), and 4.47 (2H, t, $J_{5'-4'} = 8.2$ Hz, H-5 of the 2-oxazolidinone); ^{13}C NMR ($CDCl_3$) δ 17.16 (3-Me), 27.85 (C-3), 31.80 (C-2), 38.19 (C-4), 42.31, 62.37 (C-4 and C-5 of the 2-oxazolidinone), 111.27, 112.21 (each *C*N), 153.30 (CO of the 2-oxazolidinone), and 170.46 (C-1); Mass (75 eV, rel intensity, %) *m*/*z* 222 (44, M^++1), 155 (34), 154 (base peak), 139 (13), 138 (35), 137 (72), 136 (73), 135 (10), and 107 (12). Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29%; H, 5.01; N, 19.00. Found: C, 54.46; H, 5.06; N, 18.76.
Compound **4**: Low-melting colorless solid; $[\alpha]_D^{25}$ +22.87 (84% ee estimated by chiral HPLC analysis on Daicel Chiral Cell ODH, hexane/2-propanol (4:1 v/v), 1 mL/min, t_r (minor) = 11.0 min, t_r (major) = 13.3 min, (*c* 1.28, $CHCl_3$); IR (KBr)) $\nu = 3038$, 2993, 2976, 2924, 2253 (weak, CN), 1730, 1690, 1634, 1499, 1456, 1418, 1387, 1364, 1346, 1296, 1227, 1192, 1138, 1080, 1005, 986, 910, 830, and 715 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta = 1.32$ (3H, d, $J = 6.5$ Hz, 3-Me), 2.62–2.69 (3H, m, H-2 and H-3), 4.28 (1H, d, $J_{4-3} = 4.8$ Hz, H-4), 5.15 (2H, dd, $J_{gem} = 15.5$ Hz, CH_2Ph), and 7.36–7.38 (5H, m, Ar); ^{13}C NMR ($CDCl_3$) $\delta = 17.03$ (3-CH_3), 27.82 (C-3), 32.40 (C-2), 37.08 (C-4), 67.15 (CH_2Ph), 111.19, 112.01 (each *C*N), 128.41, 128.69, 128.75 (Ar), 135.04 (q-C of Ar), and 170.54 (C-1); mass (75 eV, rel intensity, %) *m*/*z* 242 (10, M^+), 108 (81), 107 (24), 91 (base peak), 90 (17), 77 (10), and 65 (11). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.29; H, 5.87; N, 11.40.
6. Malononitrile repeats two Michael additions to give the 2:1 adduct when 1-crotonoyl-3,5-dimethyl- pyrazole is used as electrophile, while the 1:1 adduct is the only product obtained in the reaction with 3-crotonoyl-2-oxazolidinone, indicating the former is more reactive than the latter.
7. Acetic anhydride was employed to capture 3,5-dimethylpyrazole as 1-acetyl derivative. Without this acetylating agent, both the yields and enantioselectivity of adducts **17**, **18** are much decreased.[1e]