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The Asymmetric Addition of Malononitrile to α,β-Unsaturated Ketones Catalyzed by $RuCl_2[(R,R)\text{-DPEN}](PPh_3)_2$ as the Precatalyst

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Abstract

Non-borohydride ruthenium complex, $RuCl_2[(R,R)\text{-DPEN}](PPh_3)_2$ (**1f**), was demonstrated to catalyze asymmetric Michael addition of malononitrile to acyclic enones with weak bases. Michael addition of malononitrile to chalcone and analogues was promoted by combining CsOAc with CsOH in the presence of **1f** and gave good yields and up to 82% ee.

***Keywords*:** Asymmetric catalysis; Michael addition; Malononitrile; Acyclic enone; Ruthenium diamine complex

The stereoselective formation of carbon-carbon bonds is of central importance for modern organic synthesis, and the conjugate addition of carbanion nucleophiles to α,β-unsaturated carbonyl compounds represents one of the best-established construction strategies for this purpose. Thus the development of asymmetric catalytic versions of this type of transformation has been the subject of intensive research over the past several years.[1] Although substantial progress has been realized in this field, examples employed malononitrile as nucleophiles are relatively less explored and most of them don't achieve high enantioselectivity, probably owing to its incapability of two-point binding with catalysts.[2] Malononitrile is an equivalent to a 1,3-dicarbonyl compound

and the nitrile group is a versatile functional group for further elaboration.[2n-t,3] Therefore, the development of efficient Michael addition involved malononitrile is still highly desirable.

On the other hand, chiral ruthenium complexes have been successfully applied to promote enantioselective Michael addition by Ikariya[4] and Morris[5] since Suzuki's initial investigation in Michael reaction of α-keto esters and methyl vinyl ketone.[6] The Michael addition of malonates was achieved with prochiral cyclic enones[4a-c,f] (up to 99% ee) and nitroalkenes[4d] (up to 98% ee) to afford the desired adducts in excellent enantioselectivities catalyzed by the 16-electron ruthenium complexes **1a** and **1b** (Figure 1), respectively. The similar transformation was accomplished by Morris group using ternary catalyst of the binap, aminophosphine-ruthenium hydride borohydride Complex **1d** (97% ee) and ruthenium hydride borohydride Complex **1e** with chiral phosphinite and diamine ligands (90% ee) (Figure 1).[5] All these ruthenium complexes have exhibited excellent performance in case of cyclic enones, however, unsatisfactory results were observed when linear α, *β*-unsaturated ketones were adopted.[6] As a result, expanding the scope of the efficient asymmetric Michael reaction with respect to acyclic α,*β*-unsaturated enones catalyzed by ruthenium complexes would represent an important advance. Based on our group continuous work on asymmetric conjugated reduction and understanding of the Ru-diamine complexes,[7] we are interested in the possibility of employing air- and moisture-stable Ru-diamine complexes to promote the Michael addition of malononitrile and acyclic enones. Also, as part of our continuous effort to develop the catalytic asymmetric Michael reaction of malononitrile,[8] herein we would like to report an enantioselective and efficient Michael addition of malononitrile to chalcone and its analogues catalyzed by non-borohydride complex $RuCl_2[(R,R)\text{-DPEN}](PPh_3)_2$ (**1f**, DPEN = 1,2-diphenylethylenediamine) in combination with CsOAc and CsOH.

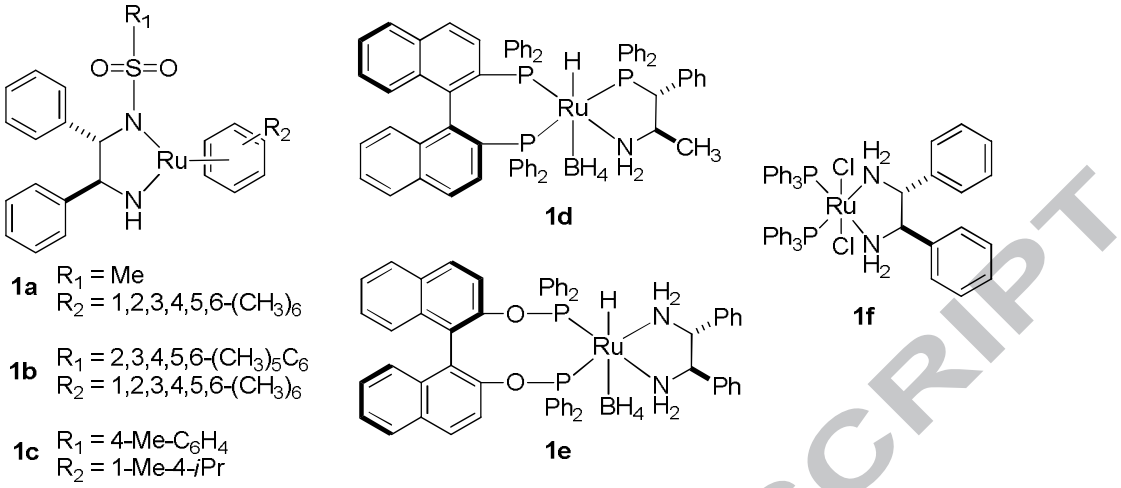


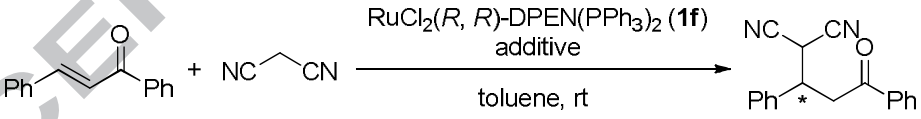
Figure 1. The well-designed Ru-complexes for asymmetric Michael addition.

Our study commenced with the preparation of 18-electron Ru-complex **1f** (Figure 1), after stirring the metal precursor $RuCl_2(PPh_3)_3$ and chiral ligand (*R*,*R*)-DPEN in THF under Argon, the desired complex **1f** was obtained and its structure was confirmed as $RuCl_2$[(*R*,*R*)-DPEN]$(PPh_3)_2$ based on single-crystal X-ray analysis, which is consistent with Ding's report.[9] We were pleased to find that **1f** in combination with *t*-BuOK [10] exhibited high catalytic activity for the asymmetric Michael addition of malononitrile **2** to chalcone **3a**[2e,2i,2n,8,11] in toluene,[12] the desired adducts **4a**[13] was cleanly isolated with 40% ee almost in quantitive yield (Table 1, entry 1). Noticeably, Morris attained racemic adduct in the case of Michael addition of dimethylmalonate to 2-cyclohexene-1-one catalyzed by complex **1d** in combination with *t*-BuOK.[5a] At the same time, we examined the enantioselectivity of 16-electron Ru-complex **1c** (Figure 1) toward the Michael addition of malononitrile **2** and chalcone **3a** in 1 mL of toluene at 15 ^{o}C and only racemic adduct was detected regardless of its well-defined performance in the Michael addition of cyclic ketones.[4a-c,f] Encouraged by this finding, we subsequently screened the inorganic base additives with **1f**.[10] It turned out that the additives had a remarkable influence on the enantioselectivity and reactivity and this transformation hardly proceeded in the absence of additive.[12] As illustrated in Table 1, the bases containing inorganic anions displayed a better reactivity than those additives containing organic anions, however, higher enantioselectivities were achieved with the latter additives (entries 5–7 *vs* entries 2–4). CF_3CO_2K was not catalytically active maybe due of too weak basicity (entry 8). The reaction was also significantly influenced by cationic ions of the

additives (entries 5 and 9–11). The reactivity increased in the order of LiOAc < CsOAc < NaOAc < KOAc. Compared with other additives, KOAc was much more enantioselective and furnished the corresponding adduct with 63% ee (entry 5), however, it remained less reactive and cost 54 h to completely consume the starting substrates. We hypothesized that mixing KOAc and KOH could result in high reactivity and enantioselectivity.[14] The Michael addition was indeed much more reactive after adding a mixture of KOH and KOAc at different ratio, but the ee decreased in comparison with KOAc (entries 12-14 *vs* entry 5). Compared with KOH, higher enantioselectivity (55% ee) was obtained by using CsOH as a base (entry 15 *vs* entry 2). Thus, we further investigated the effect of a mixture of CsOH and CsOAc, to our delight, it remained the high reactivity and afforded the desired adduct with comparable ee (entries 16-18). When CsOH and CsOAc were added at the ratio of 1 : 2, an adduct **4a** was obtained in 56% ee and almost quantitive yield after 4 h (entry 18). The transition metal additive was also used but no desired adduct was attained even after 96 h in the presence of $Ni(OAc)_2$, which could coordinate to the carbonyl oxygen and the olefin π-bond in the *s*-cis conformation[15] (entry 19). While organic bases were used as an additive, the conjugate addition occurred smoothly with (*R*,*R*)-DPEN and TEA (TEA = triethylamine), but considerably reduced enantioselectivities were observed (entries 20 and 21).

Table 1

Additive screening studies of asymmetric Michael addition of malononitrile **2** to chalcone **3a**[a]



3a **2** **4a**

Entry	Additive	t (h)	Yield (%)[b]	Ee (%)[c]
1	*t*-BuOK	18	99	40
2	KOH	48	97	44
3	K_2CO_3	7.5	99	30
4	$KHCO_3$	15	99	38
5	KOAc	54	99	63
6	$PhCO_2K$	96	45	55
7	HCO_2K	80	99	54
8	CF_3CO_2K	96	NR	/
9	LiOAc[d]	96	26	31

10	NaOAc	70	90	41
11	CsOAc	72	81	50
12	KOH/KOAc = 2:1	2	99	51
13	KOH/KOAc = 1:1	2	99	52
14	KOH/KOAc = 1:2	2	99	51
15	CsOH[d]	48	99	55
16	CsOH[d]/CsOAc = 2:1	4	99	52
17	CsOH[d]/CsOAc = 1:1	4	99	55
18	CsOH[d]/CsOAc = 1: 2	4	99	56
19	$Ni(OAc)_2$[d]	96	nr	/
20[e]	(*R*,*R*)-DPEN	70	99	42
21	Et_3N	96	64	8

[a]Unless otherwise noted, all of the reactions were performed with 0.1 mmol of **3a**, 0.16 mmol of malononitrile, 10 mol% of **1f** and 30 mol% of additive in 2 mL of toluene at 24 °C.

[b]Isolated yield after flash chromatography on silica gel.

[c]Determined by HPLC on chiral OD column.

[d]The available hydrate was directly used.

[e]With (*R*,*R*)-DPEN (30 mol%) in the absence of **1f**, **4a** was obtained only in 10% yield and 6% ee after 24 h.[16]

Subsequently, we kept the ratio of $CsOH·H_2O$ and CsOAc constant (CsOH/CsOAc = 1 : 2) and investigated the effect of the loading of additives on the enantioselectivity and reactivity. As illustrated in Table 2, the enantioselectivity was somewhat influenced by the quantities of the additives (entries 1–5). Gratifyingly, the addition product **4a** was formed with 61% ee in the presence of 45 mol% additives (entry 4). We conducted the Michael reaction at lower temperature to improve the enantioselectivity and pleased to find that a higher ee (73% ee) was obtained at –10 °C (entry 7). Further lowering the temperature to –20 °C resulted in marginal increase in enantioselectivity (entry 8). In the hope of further enhancing the enantioselectivity, the other ruthenium complexes containing diamine and diphosphine ligands (Figure 2) were employed and the results were presented in Table 2 (entries 10–15). The reactions were carried out in the presence of 5 mol% catalyst in toluene at –10 °C. The complexes **1g** and **1h**, generated with (*R*)- and (*S*)-binap respectively,[17] provided the desired adduct in 91% and 90% yield and lower ee values after 70 h (entries 10 and 11). It was noteworthy that they afforded **4a** with same configuration in spite of the opposite configuration of the phosphine ligand. The results obviously

indicated that the chiral diamine played a crucial role in the asymmetric induction. Enlightened by this observation, this transformation was then conducted in the presence of the novel ruthenium complex containing (*R*,*R*)-DACH (DACH = 1,2-cyclohexanediamine) (Figure 2, **1i**). Unfortunately, no beneficial effect was observed in terms of enantioselectivity (17% ee) although it exhibited high reactivity (entry 12). Furthermore, the ruthenium complexes containing modified phosphine ligands[9] (Figure 2, **1j** and **1k**) had been applied in the conjugate addition. The Michael addition proceeded smoothly to afford **4a** in 50% ee and 96% yield with **1j**, but no desired adduct was attained with **1k**, probably due to steric hindrance of the bulky phosphine ligand (entries 13 and 14). Noticeably, we explored the mixed catalysts consisting of diastereomers of **1l**[18] and **4a** was obtained with poorer enantioselectivity in the presence of them (entry 15). As a result, **1f** was the best choice of the catalyst for the present reaction.

Table 2

Asymmetric Michael addition of malononitrile **2** to chalcone **3a** with various catalysts under different conditions[a]

Entry	CsOH/CsOAc (1:2, mol %)	Catalyst	T (^{o}C)	t (h)	Yield (%)[b]	Ee (%)[c]
1	20	**1f**	24	4	99	56
2	30	**1f**	24	4	99	56
3	40	**1f**	24	4	97	60
4	45	**1f**	24	4	99	61
5	50	**1f**	24	4	99	54
6	45	**1f**	0	12	99	66
7	45	**1f**	–10	24	99	73
8	45	**1f**	–20	48	96	74
9[d]	45	**1f**	–10	30	95	72
10[d]	45	**1g**	–10	70	91	47
11[d]	45	**1h**	–10	70	90	37
12[d]	45	**1i**	–10	24	80	17
13[d]	45	**1j**	–10	48	96	50
14[d]	45	**1k**	–10	90	NR	/
15[d]	45	**1l**	–10	48	70	21

[a]Unless otherwise noted, all of the reactions were performed with 0.1 mmol of **3a**, 0.16 mmol of malononitrile, 10 mol% of Ru-complex in 2 mL of toluene.

[b]Isolated yield of **4a** after flash chromatography on silica gel.

[c]Determined by HPLC on chiral OD column.

[d]Perform with 5 mol% of catalyst.

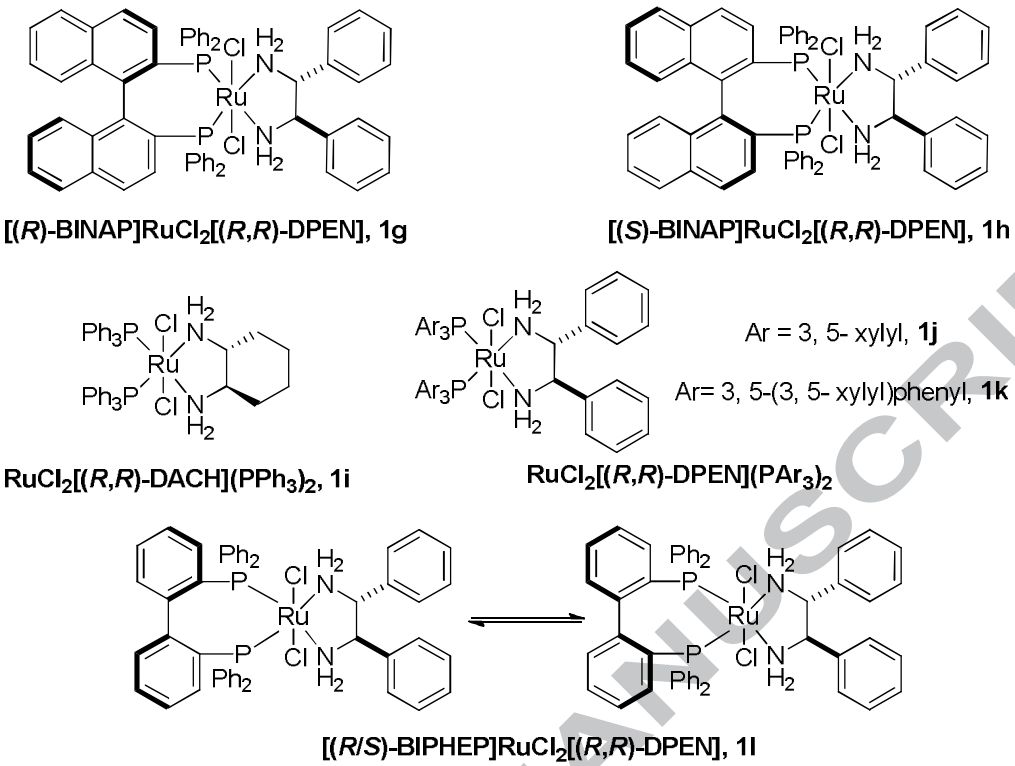


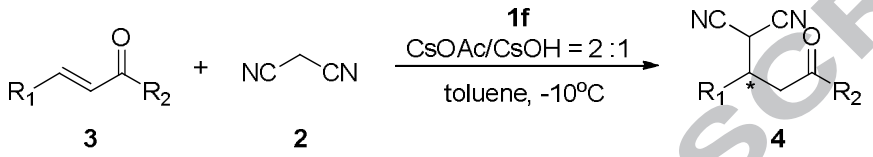
Figure 2. The structure of the ruthenium complexes.

With the optimal reaction condition in hand,[12] we then examined a variety of α,β-unsaturated ketones to establish the general utility of the catalytical transformation. As illustrated in Table 3, chalcone analogues bearing various substitutes on the aryl ring proceeded smoothly at –10 ^{o}C in the presence of **1f** (10 mol%), CsOAc (30 mol%) and $CsOH{\cdot}2H_2O$ (15 mol%), providing the desired products **4b–g** with moderate to good enantioselectivities (entries 1–7). The enantioselectivities and reactivities were dependent upon the electronic properties of substituted groups. **3c** and **3e** with electron-withdrawing substituents on aryl ring proceeded with higher enantioselectivities and reactivities than **3b** and **3d** with electron-donating substituents (entries 3 and 5 *vs* entries 2 and 4). The highest enantioselectivity (82% ee) was obtained in the case of the nitro-derivative **3c** (entry 3). Moreover, the reaction was remarkably influenced by sterical hindrance, **3g** furnished the desired product **4g** only in 30% ee and 18% yield even after prolonged time (entry 7). **3h** with 2-naphthyl group on terminal double bond occurred smoothly and satisfactory enantioselectivity was obtained (71% ee, entry 8). Furthermore, heteroaryl enones **3i** and **3j** underwent clean reaction as well, and afforded the corresponding adducts **4i** and **4j** with 65% and 67% ee, respectively (entries 9 and 10). In addition, chalcone and diethyl malonate (**5**)

occurred smoothly at room temperature and furnished the adduct **6**[11] with 33% ee and 77% yield after 40 h (Scheme 1). However, when the unsaturated ketone bears an aliphatic group, no reaction occurs for 4-phenylbut-3-en-2-one (**3k**) at 24 °C (entry 11). Moreover, cyclohex-2-enone (**3l**) gave 72% yield for 100 h but only 6% ee (entry 12).

Table 3

Asymmetric Michael addition of malononitrile **2** to α,β-unsaturated ketones **3**[a]



Entry	R_1	R_2	Substrate	Product	Time (h)	Yield (%)[b]	Ee (%)[c]
1	C_6H_5	C_6H_5	**3a**	**4a**	24	99	73[d]
2	C_6H_5	*p*-$CH_3OC_6H_4$	**3b**	**4b**	70	55	70
3	C_6H_5	*p*-$NO_2C_6H_4$	**3c**	**4c**	24	93	82
4	*p*-$CH_3OC_6H_4$	C_6H_5	**3d**	**4d**	70	73	64
5	*p*-$NO_2C_6H_4$	C_6H_5	**3e**	**4e**	24	95	68
6	*p*-FC_6H_4	C_6H_5	**3f**	**4f**	70	90	72
7	1,3,5-$(CH_3)_3C_6H_2$	C_6H_5	**3g**	**4g**	70	18	30
8	2-naphthyl	C_6H_5	**3h**	**4h**	70	98	71
9	2-thienyl	C_6H_5	**3i**	**4i**	70	50	66
10	C_6H_5	2-furanyl	**3j**	**4j**	24	97	67
11[e]	C_6H_5	CH_3	**3k**	**4k**	70	/[f]	/[f]
12[e]	-$(CH_2)_3$-		**3l**	**4l**	100	72	6

[a]Unless otherwise noted, all of the reactions were performed with 0.1 mmol of **3a**, 0.16 mmol of malononitrile, 10 mol% of **1f**, 30 mol% CsOAc and 15 mol% $CsOH·H_2O$ in 2 mL of toluene at –10 °C.

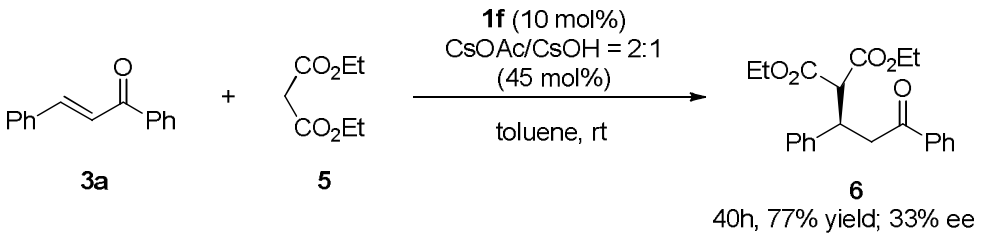
[b]Isolated yield after flash chromatography on silica gel.

[c]Determined by HPLC on chiral column.

[d]The absolute configuration of **4a** was (*R*)-form determined by comparison of the specific optical rotation with that reported in the literature,[13a] and the other adducts were assigned accordingly.

[e]At 24 °C.

[f]No reaction.



Scheme 1. The Michael addition of chalcone and diethyl malonate.

In summary, we have developed a novel ruthenium-catalyst system for asymmetric Michael addition of acyclic enones. In combination with CsOAc and CsOH, $RuCl_2[(R,R)\text{-DPEN}](PPh_3)_2$ can effectively promote the Michael addition of malononitrile to chalcone and analogues in high yields with moderate to good entantioselectivities (up to 82% ee). To the best of our knowledge, this is the first example that ruthenium complex is used to promote Michael addition of malononitrile to α,β-unsaturated carbonyl compounds especially acyclic enones. It is also notable that the reactivity can be greatly improved after adding the mixed bases. At the same time, new ruthenium complexes are prepared and applied to this asymmetric transformation. Further investigation into the reaction mechanism is under the way.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.

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12. Other solvents (*N*,*N*'-Dimethylformamide, Acetonitrile, Tetrahydrofuran, Dichloromethane, *tert*-Butanol, Benzene) displayed inferior enantioselectivities comparing with toluene when the corresponding Michael addition was performed in the presence of 10 mol % **1f** and 30 mol% (*R*,*R*)-DPEN. In the absence of base, very low activity was observed with only complex **1f** (9% yield and 14% ee for 137 h).
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16. When 10 mol% $RuCl_2(PPh_3)_3$ and 30 mol% (*R*,*R*)-DPEN were used to prepare the catalyst *in situ*, 70% yield and 57% ee of **4a** was obtained for 21 h. (*R*)-1,1'-Binaphthalene-2,2'-diamine, (*S*)-pyrrolidin-2-ylmethanamine, (1*R*,2*R*)-1,2-dicyclohexylethane-1,2-diamine, and (1*R*,2*R*)-1,2-bis(4-methoxyphenyl)ethane-1,2-diamine (*p*-MeODPEN) were also tested in the conditions and only less than 8% ee of **4a** was gained except *p*-MeODPEN, which gave 59% ee but lower reactivity (60% yield, 70 h).

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Graphical Abstract

The Asymmetric Addition of Malononitrile to α,β-Unsaturated Ketones Catalyzed by $RuCl_2[(R,R)\text{-DPEN}](PPh_3)_2$ as the Precatalyst

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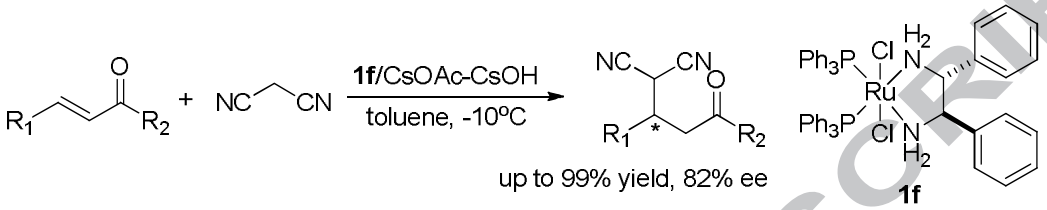

up to 99% yield, 82% ee

1f