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COMMUNICATION

Base promoted synthesis of activated cyclopropanes bearing homologated carbonyl groups *via* tandem Michael addition–intramolecular enolate trapping†

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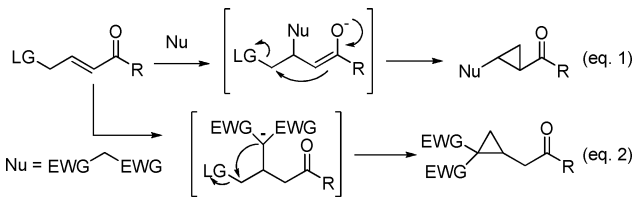
A simple base promoted intramolecular Michael initiated ring closure reaction of γ-hydroxyenone derived diphenyl phosphinates with 1,3-indandione, enabled the synthesis of novel activated cyclopropanes with homologated carbonyl moiety in good yield. Promising levels of enantioselectivity are achieved when using cinchona derivatives as promoters.

The development of methods that enable access to structurally diverse cyclopropane containing compounds is an important goal in synthetic organic chemistry. Indeed, cyclopropanes are amongst the most useful class of versatile building blocks[1] and several biologically active molecules contain the cyclopropane unit.[2] Recently, an increasing interest has been devoted to the synthesis of activated cyclopropanes bearing geminal electron-withdrawing groups, which are synthetically versatile products.[3] These electrophilic compounds undergo facile ring opening with nucleophiles to afford homologous Michael addition adducts and have found application in the synthesis of heterocycles by ring expansion reactions.[1,4]

The Michael initiated ring closure (MIRC) reaction,[5] is an attractive strategy to construct the cyclopropane unit, which has been largely exemplified by the reaction of electron-poor alkenes with carbon nucleophiles bearing a suitable leaving group.[6]

Given our interest in Michael addition reactions[7] and in MIRC reactions leading to epoxides,[8] we turned our attention to the synthesis of activated cyclopropanes through a less investigated MIRC approach (Scheme 1).



Scheme 1

According to the tandem process depicted in eq. 1, the conjugate addition of a carbon nucleophile can also proceed onto an α,β-unsaturated carbonyl compound bearing an internal leaving group at the γ-position.[9] Then, the enolate reacts *via* intramolecular S_N2 alkylation to afford the 1,2-disubstituted cyclopropane. This approach has been exploited by reacting, at low temperatures, conjugated γ-haloenoates with metal-enolates and organometallic reagents. Competition with the direct S_N2 displacement often affords a mixture of the cyclopropane and the alkylation by-product.[10] Recently, an elegant enantioselective example of this transformation has been reported by Feringa and co-authors.[11] *trans*-1,2-Disubstituted cyclopropanes were obtained with high ee by reacting 4-chloro-α,β-unsaturated carbonyl compounds with Grignard reagents in the presence of CuI/Tol-BINAP as the catalytic system.

We envisaged that when using a methylene active compound as the nucleophile (eq. 2), the most stable enolate, formed after proton transfer, would react affording the cyclopropane with a homologated carbonyl moiety.[12] Homologation of carbonyl compounds by one carbon extension is a challenging transformation in organic synthesis and only a few effective methods exist.[13] Herein, we report the feasibility of the MIRC approach illustrated in eq. 2 of Scheme 1 for the synthesis of activated cyclopropanes, bearing homologated carbonyl groups.[14] These compounds have been selectively synthesized in good yields by K_2CO_3 promoted tandem reaction of γ-hydroxyenone derived diphenyl phosphinates with 1,3-indandione. The process appears to be suitable for extension to other methylene active compounds. Preliminary findings show that the tandem process proceeds in enantioselective manner when using cinchona alkaloids.

γ-Hydroxyenone derived diphenyl phosphinates were chosen as starting compounds to check the process. The suitability of this type of leaving group in the synthesis of cyclopropanes, *via* a different approach, has been previously addressed.[15] Initial attempts commenced with an examination of 1,3-dicarbonyl compounds as the selected nucleophiles. Differently *O*-protected γ-hydroxyenones were reacted with an array of 1,3-dicarbonyl compounds in chloroform using organic bases or K_2CO_3[16] as base at room temperature (Table 1).

Linear 1,3-dicarbonyl compounds did not react when using Et_3N or K_2CO_3 (entries 1–4). The nature of the base proved to be

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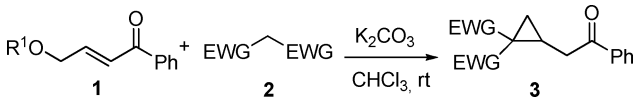
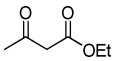
Table 1 Screen of 1,3-dicarbonyl compounds and protected γ-hydroxyenones in the base-promoted MIRC reaction[a]



Entry	R^1	2	Base	Time (h)	Yield (%)[b]
1	$P(Ph)_2$ **1a**		Et_3N	16	—
2	"	"	K_2CO_3	16	—
3	"		Et_3N	16	—
4	"	"	K_2CO_3	16	—
5	$P(Ph)_2$ **1a**		K_2CO_3	16	—
6	"	"	Et_3N	16	—
7	"	"		16	31
8	$P(OEt)_2$ **1b**	"		24	30
9	$P(Ph)_2$ **1a**		K_2CO_3	14	64
10	$P(OEt)_2$ **1b**	"	K_2CO_3	16	49
11	$P(OPh)_2$ **1c**	"	K_2CO_3	16	30
12	$P(Ph)_2$ **1a**		K_2CO_3	15	—
13	$P(Ph)_2$ **1a**		K_2CO_3	15	—

[a] Experimental conditions: the reaction was carried out in a 0.1 mmol scale in 2 mL of $CHCl_3$ with a 1 : 1.1 : 1 ratio of **1** to **2** to base. [b] Yield of isolated product.

critical as observed when using Meldrum's acid as the nucleophile (entries 5–8). The expected cyclopropane **3a** was formed with 2-piperidinemethanol as the base with diphenyl phosphinate **1a** and diethyl phosphate **1b** in comparable yields (entries 7 and 8). In contrast, 1,3-indandione afforded cyclopropane **3b** in the presence of K_2CO_3 with all differently *O*-protected γ-hydroxyenones **1a–c** (entries 9–11).

The best yield was achieved when using the diphenyl phosphinate derivative **1a** (entry 9). Disappointingly, cyclic 1,3-cyclohexandione and 1,3-cyclopentandione did not yield the desired product under optimal conditions found for 1,3-indandione (entries 12 and 13). Overall, these data indicate that the formation of the cyclopropane is feasible, although optimization of the reaction conditions are required for each methylene active compound checked.[17]

A more detailed study on the nature of the base and solvent was next pursued selecting the reaction of 1,3-indandione with compound **1a** (Table 2).

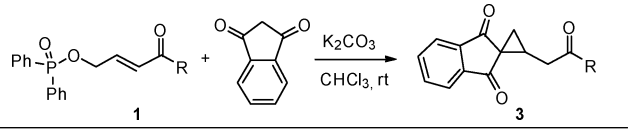
Table 2 Solvent and base effect on the MIRC reaction of compound **1a** with 1,3-indandione at room temperature[a]

Entry	Base	Solvent	Time (h)	Yield **3b**(%)[b]
1	Et_3N	$CHCl_3$	29	—
2	DBU	$CHCl_3$	14	trace
3	2-piperidinemethanol	$CHCl_3$	18	20
4	AcONa	$CHCl_3$	16	—
5	*t*BuOK	$CHCl_3$	15	26
6	Cs_2CO_3	$CHCl_3$	17	56
7	K_2CO_3	CH_2Cl_2	16	54
8	K_2CO_3	toluene	16	22
9	K_2CO_3	AcOEt	15	40
10	K_2CO_3	THF	16	52

[a] Experimental conditions: the reaction was carried out in a 0.1 mmol scale in 2 mL of solvent with a 1 : 1.1 : 1 ratio of **1** to 1,3-indandione to base. [b] Yield of isolated product.

Organic bases proved to be scarcely active (entries 1–5). The ^{1}H-NMR analysis of the reaction mixture with Et_3N in $CDCl_3$

Table 3 K_2CO_3-promoted MIRC reaction of compounds **1** with 1,3-indandione[a]



Entry	R	Time (h)	3	Yield (%)[b]
1	Ph (**a**)	14	**3b**	64
2	4-$CF_3C_6H_4$ (**d**)	17	**3c**	73
3	4-ClC_6H_4 (**e**)	16	**3d**	96
4	3-ClC_6H_4 (**f**)	17	**3e**	81
5	2-ClC_6H_4 (**g**)	16	**3f**	37
6	4-$MeOC_6H_4$ (**h**)	17	**3g**	79
7	2-naphthyl (**i**)	15	**3h**	63

[a] Experimental conditions: the reaction was carried out in a 0.1 mmol scale in 2 mL of $CHCl_3$ with a 1 : 1.1 : 1 ratio of **1** to 1,3-indandione to K_2CO_3. [b] Yield of isolated product.

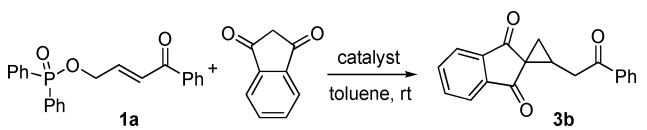
was carried out at different times. After 15 h, compound **1a** was still largely present together with some minor unidentified side-products. The reaction proceeded in a similar way when replacing K_2CO_3 with Cs_2CO_3 (entry 6), indicating a slight effect of the nature of the cation on the process. Screening of different solvents when using K_2CO_3 as the base confirmed $CHCl_3$ as the best medium (entries 7–10).

The scope of the tandem process with an array of compounds **1** under optimal reaction conditions was studied (Table 3).

Cyclopropanes **3** were obtained in good yields irrespective of the type of substitution on the aromatic ring in the starting reagent **1**, except when using the 2-chloro substituted derivative **1g** which furnished product **3f** in 37% yield (entry 5).[18]x

With a view to developing an enantioselective cyclopropanation, a preliminary investigation on the model reaction, using some bifunctional organocatalysts, was carried out in toluene at room temperature (Table 4).

Table 4 Preliminary study on the asymmetric MIRC reaction of model compound **1a** with 1,3-indandione[a]



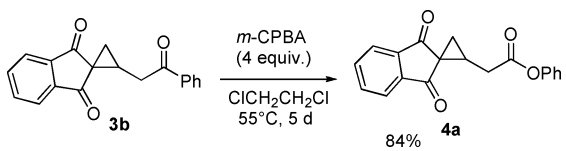
Entry	Catalyst	Additive	Time (h)	Yield (%)[b]	ee (%)[c]
1	CD	—	1.5	65	29
2	QN	—	1.5	72	34
3	HQD	—	1.5	62	–51
4	eQNT	—	1.5	80	60
5	eHQNT	—	1.5	89	65
6[d]	eHQNT	Et_3N	14	53	62
7[d]	eHQNT	DMAP	15	53	61
8[d]	eHQNT	$KHCO_3$	14	33	67
9[e]	eHQNT	NaOAc	16	56	67

[a] Experimental conditions: the reaction was carried out in a 0.1 mmol scale in 2 mL of toluene with a 1 : 1.1 : 1 ratio of **1a** to 1,3-indandione to catalyst. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 30 mol% of eHQNT and 50 mol% of base. [e] 30 mol% of eHQNT and 1 equiv of base in 1 mL of toluene.

We assumed them to be more effective promoters than simple organic bases thanks to the plausible activation of both reagents.[19] Interestingly, when using stoichiometric loadings of cinchonidine (CD), quinine (QN) and hydroquinidine (HQD) (entries 1–3) compound **3b** was isolated in satisfactory yield and up to 51% ee after short reaction times. In the presence of 9-amino-9-deoxy-*epi*-quinine derived thiourea (eQNT) and 9-amino-9-deoxy-*epi*-hydroquinine derived thiourea (eHQNT), bifunctional thioureas successfully developed by different groups for carbon–carbon bond formation reactions,[20] product **3b** was isolated in high yield and improved ee (entries 4 and 5). In order to ascertain the feasibility of a catalytic version, some basic additives were added in the presence of 30 mol% of eHQNT to remove the acid formed as by-product (entries 6–9).

Pleasingly, the different additives did not affect enantioselectivity and NaOAc enabled the isolation of compound **3b** in satisfactory yield and up to 67% ee (entry 9). Although the levels of enantioselectivity need to be improved, these promising insights suggest that the development of a highly enantioselective catalytic process will be likely attainable through a proper choice of the bifunctional organocatalyst/basic additive couple.

Finally, to prepare synthetically more useful derivatives, we tried to differentiate the ketonic groups of cyclopropanes **3** *via* Baeyer–Villiger oxidation. Compound **3b** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) in 1,2-dichloroethane at 55 °C (Scheme 2).



Scheme 2 Baeyer–Villiger oxidation of cyclopropane **3b**.

Pleasingly, the selective formation of the phenyl ester **4a** was achieved, thus enabling the access to activated cyclopropanes bearing different homologated carbonyl moieties. Moreover, it has to be noted that products **3** and **4** are potentially amenable to stereocontrolled α-functionalization of the carbonyl group, with the generation of cyclopropanes bearing two contiguous chiral centers.[21]

In conclusion, we have illustrated a facile approach to novel activated cyclopropanes bearing a homologated carbonyl group, *via* a MIRC strategy, which features an intramolecular enolate trapping. Promising levels of enantiocontrol are attainable when employing cinchona alkaloids and their derivatives as the promoters. Synthetic manipulation of the cyclopropanes can lead to diversified products. Studies are currently focused on the extension of this MIRC reaction to other methylene active compounds and acceptors and on the development of an asymmetric catalytic version.

Acknowledgements

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