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Asymmetric synthesis of activated cyclopropanes catalyzed by cinchonidine as a chiral Brønsted base

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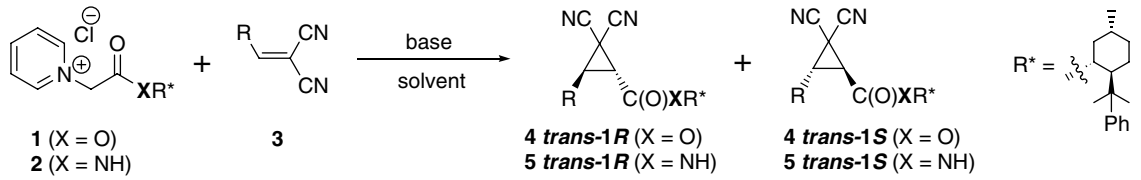
Dedicated to Professor Kin-ya Akiba on the occasion of his 70th birthday

Abstract—Cinchonidine catalyzed the cyclopropanation reaction between chloromethyl ketones and β-substituted methylidenemalononitriles to give *trans*-cyclopropanes with enantioselectivity up to 82% ee. Experimental evidence suggests that cinchonidine functions as a chiral Brønsted base catalyst in the reaction and hydrogen bonding is essential for inducing high enantioselectivity.

The versatility of cyclopropanes has made them useful building blocks in organic synthesis[1] and certain cyclopropanes have been found to show unique bioactivity.[2] For this reason there is an abundance in the literature on the asymmetric synthesis of this unique group of compounds.[3] High levels of asymmetric induction have been achieved for catalytic reactions involving metal-carbenoid reactions with aryl-substituted and electron-rich olefins.[4] As for electron-deficient olefins, Michael-type reactions have been the methods of choice.[3] For the preparation of cyclopropanes that bear multiple numbers of electron-withdrawing groups, which would be valuable for further functionalization, high levels of catalytic asymmetric induction have been achieved in only a limited number of reports.[5–8] Especially for cyclopropanes bearing three of such substituents, there is only one isolated example, which involves an intramolecular cyclization process.[8] In connection with our long interest in the chemistry of small ring compounds, cyclopropanes[9] and epoxides,[10] we have recently reported on the diastereoselective cyclopropanation reaction using pyridinium ylides bearing either 8-phenylmenthol (**1**) or 8-phenylmenthylamine (**2**) as the chiral auxiliary with β-substituted methylidenemalononitriles (**3**) to give highly functionalized cyclopropanes (**4**,**5**), which bear an additional fourth substituent, with diastereoselectivity up to 96% de (Scheme 1).[11] In an attempt to advance this reaction to a catalytic process, we have found that cinchona alkaloids function as Brønsted base catalysts in the reaction between chloromethyl ketones and β-substituted methylidenemalononitriles to give highly functionalized cyclopropanes



1 (X = O)
2 (X = NH)
3
4 ***trans*-1*R*** (X = O)
5 ***trans*-1*R*** (X = NH)
4 ***trans*-1*S*** (X = O)
5 ***trans*-1*S*** (X = NH)

Scheme 1.

Keywords: Enantioselective; Activated cyclopropane; Cinchonidine; Brønsted base catalyst; Methylidenemalononitrile.
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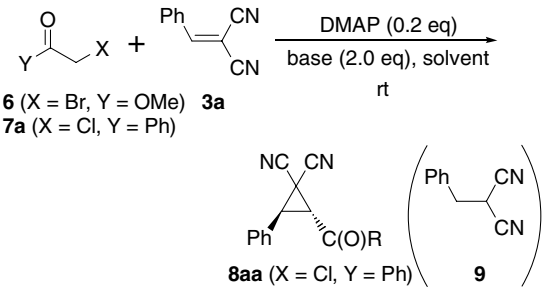
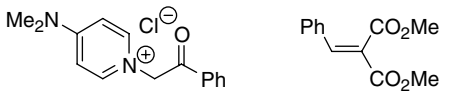


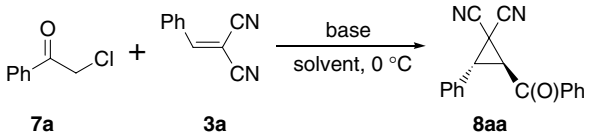
Scheme 2.

with enantioselectivity up to 82% ee. Herein, we present our results.

In the final cyclopropane ring-closing step of the reaction involving pyridinium ylides, pyridine is released as a leaving group. This suggested that if a halomethylcarbonyl compound could react with a certain substituted pyridine with sufficient reactivity to form a pyridinium salt and the halomethylcarbonyl compound itself did not react directly with the Michael acceptor, a catalytic reaction could be realized. Thus, we examined 4-methoxy- and 4-dimethylamino-pyridine as possible candidates for the catalytic reaction. The examination was carried out using the substituted pyridine (0.2 equiv) in combination with a stoichiometric inorganic base used in excess (Scheme 2). 4-Methoxypyridine was found not to be an efficient catalyst, giving the desired compound in only less than 10% yield at best. In the case of 4-dimethylaminopyridine (DMAP), when bromoacetic ester **6** was used, the major product was found to be compound **9** resulting from double bond reduction of the Michael acceptor, likely via electron transfer from the electron rich anion. However, when phenacyl chloride **7a** was used, the catalytic reaction was found to proceed giving the expected tetra-substituted cyclopropane **8** (CH_3CN, 1d, 61%; CH_2Cl_2, 2d, 52%). In order to confirm that the reaction proceeded via the intermediacy of a pyridinium ylide, pyridinium salt **10** was prepared from DMAP and phenacyl chloride, and was subjected to the cyclopropanation reaction. However, results similar to those of the catalytic reaction could not be reproduced, giving the reduced product **9** as the major product instead. This distinction suggested that in the catalytic reaction, DMAP was functioning not as a Lewis base but as a Brønsted base. To this end, we examined several other amine bases, namely 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (CH_3CN, 1d, 42%), 1,4-diazabicyclo[2.2.2]octane (DABCO) (CH_3CN, 2d, 73%), and Et_3N (CH_3CN, 2d, 59%), as catalysts in the presence of Na_2CO_3 as the stoichiometric base and found that all were equally effective as long as a large amount of water was not present. In cases with water, a complex mixture, evidently caused by decomposition of the product cyclopropane, was obtained. The ester analog of the Michael acceptor, β-substituted alkylidenemalonate **11**, was not reactive enough and did not give rise to products. This could be due to the intrinsic size difference between the cyano group and the ester group. As in the case of DMAP, DABCO was inefficient as a catalyst for the reaction of bromoacetates.



The fact that DABCO was effective for the alkylidenemalononitriles with phenacyl chloride suggested that cinchona alkaloids that bear a similarly bicyclic quinuclidine moiety might be effective as asymmetric catalysts.[12,13] It was also found that the use of Na_2CO_3 in the absence of amine at rt also gave rise to a product, especially in polar MeCN, suggesting that a background reaction might be problematic. Thus, with the intention of minimizing background reactions, runs using stoichiometric amounts of quinine **12** and no inorganic bases were first examined at 0 °C (Scheme 3, Table 1). An examination of solvents revealed that those of lower polarity were more suitable (entries 1–4). A change from quinine to cinchonidine **13** lead to a slight rise in selectivity and thus the latter was selected for the ensuing examinations. Lowering the amount of cinchonidine to 0.2 equiv by using Na_2CO_3 as the stoichiometric base lead unexpectedly to a product with somewhat higher enantiomeric excess (up to 56% ee) than the reactions using stoichiometric amounts of the chiral amine. *O*-methyl substituted cinchona alkaloid derivatives have been reported by Gaunt and co-workers to be very efficient catalysts for the intra- and inter-molecular cyclopropanation reactions between halomethyl carbonyl



Scheme 3.

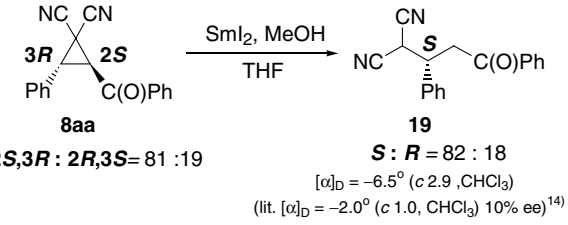
Table 1. Asymmetric cyclopropanation with chiral amines

Entry	Base	Solvent	Yield (%)	ee[a] (%)
1	**12** (1.1 equiv)	DMF	46	2
2	**12** (1.1 equiv)	MeCN	61	6
3	**12** (1.1 equiv)	CH_2Cl_2	71	24
4	**12** (1.1 equiv)	Toluene	34	30
5	**13** (1.1 equiv)	CH_2Cl_2	56	34
6	**13** (0.2 equiv), Na_2CO_3 (2.0 equiv)	CH_2Cl_2	61	40
7	**13** (0.2 equiv), Na_2CO_3 (2.0 equiv)	Toluene	78	56
8	**14** (1.1 equiv)	CH_2Cl_2	71	10
9	**15** (1.1 equiv)	CH_2Cl_2	36	−4
10	**16** (0.2 equiv), Na_2CO_3 (2.0 equiv)	Toluene	81	0
11	**17** (0.2 equiv), Na_2CO_3 (2.0 equiv)	Toluene	74	0
12	**18** (0.2 equiv), Na_2CO_3 (2.0 equiv)	CH_2Cl_2	59	18

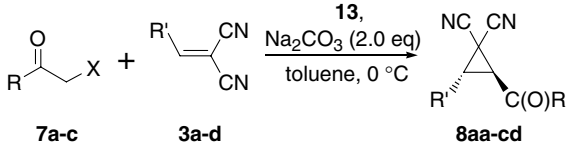
[a] Determined by HPLC (Daisel chiral OD).

compounds and Michael acceptors without a β-substituent.[6] In their case, the reaction is assumed to proceed via ylide intermediates, and elevated temperatures are actually required to effect the reaction, whereas in our case, the reaction proceeds even at 0 °C. The mechanistic variation is probably the reason for the difference in reactivity which allows for the formation of more densely substituted compounds in our case.[7] Incidentally, the quaternary ammonium salt intermediate formed by the reaction of phenacyl chloride with cinchonidine, which is anticipated in the ylide mechanism, does not form under our reaction conditions in the absence of the acceptor. This fact further supports our assumption that the Brønsted base mechanism is the one that is at work. Thus, the difference in reactivity observed between phenacyl chloride and bromoacetates can be rationalized to be due to the difference in acidity between the two.

Several simple derivatives of cinchonidine were also examined in the reaction employing phenacyl chloride and phenylmethylidenemalononitrile. Enantioselectivity

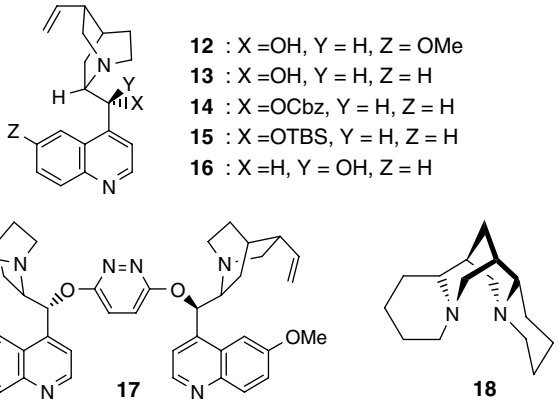


Scheme 4.



Scheme 5.

decreased greatly for compounds **14** and **15** which bear typical oxygen protecting groups, and compound **16** which has the opposite absolute stereochemistry upon the chiral carbon bearing the hydroxy group. Neither effective were bis(cinchona alkaloid) **17** or sparteine **18**. The relationship between the structure of the alkaloid and stereoselectivity implies that the presence of a hydroxy group with the appropriate stereochemistry is important. Thus, hydrogen-bonding could be operative in the selectivity determining process. The fact that enantioselectivity is higher in solvents of low polarity also suggests the requisition of hydrogen bonding for high selectivity.



The absolute stereochemistry of the major product was determined to be 2*S*,3*R*-2-benzoyl-3-phenyl-1,1-cyclopropanedicarbonitrile, by transforming an enantiomerically enriched sample of **8aa** to known compound **19**, by samarium(II) iodide reduction (Scheme 4).[14]

The scope of the reaction was examined by using several β-substituted methylidienemalononitriles and halomethyl ketones (Scheme 5, Table 2). First of all, the amount of catalyst was examined with phenacyl chloride, and it was found that the amount of catalyst could be lowered down to 1 mol % without much loss in reactivity. Actually, the enantioselectivity rose a bit with the decrease in the amount of catalyst (entries 1–4).[15]

Table 2. Asymmetric cyclopropanation of various substrates using cinchonidine as catalyst

Entry	X	R		R′		**13** (equiv)	Time (days)	Product	Yield[a] (%)	ee[b] (%)
1	Cl	Ph	**7a**	Ph	**3a**	0.2	4	**8aa**	78	56
2	Cl	Ph	**7a**	Ph	**3a**	0.05	4	**8aa**	72	60
3	Cl	Ph	**7a**	Ph	**3a**	0.01	5	**8aa**	73	62
4	Cl	Ph	**7a**	Ph	**3a**	0.001	7	**8aa**	34(50)	54
5	Br	Ph	**7a′**	Ph	**3a**	0.2	8	**8aa**	45(66)	20
6	Cl	Ph	**7a**	2-ClC_6H_4	**3b**	0.2	2	**8ab**	81	44
7	Cl	Ph	**7a**	4-Py	**3c**	0.2	6	**8ac**	23	2
8	Cl	Ph	**7a**	*t*-Bu	**3d**	0.2	3	**8ad**	27(36)	66
9	Cl	Ph	**7a**	*t*-Bu	**3d**	0.01	4	**8ad**	25(44)	82
10	Cl	2-ClC_6H_4	**7b**	Ph	**3a**	0.2	7	**8ba**	19	33
11	Cl	2-ClC_6H_4	**7b**	*t*-Bu	**3d**	0.2	6	**8bd**	71	76
12	Cl	2-ClC_6H_4	**7b**	*t*-Bu	**3d**	0.01	7	**8bd**	65(68)	82
13	Cl	*t*-Bu	**7c**	Ph	**3a**	0.2	7	**8ca**	(Trans) 6(13) (Cis) 22(51)	(Trans) 60 (Cis) 56
14	Cl	*t*-Bu	**7c**	*t*-Bu	**3d**	0.2	7	**8cd**	No reaction	—

[a] Yield base upon recovered starting material is in parentheses.
[b] Determined by HPLC (Daisel chiral OD).

Phenacyl bromide turned out to be much less effective compared with the corresponding chloride (entry 5). As for other Michael acceptors in combination with phenacyl chloride, the somewhat hindered 2-chlorophenyl substituted acceptor gave rise to somewhat lower enantioselectivity and there was no induction for the highly electronegative 4-pyridyl substituted olefin (entries 6 and 7). As for the *t*-Bu acceptor, there was rather a large increase in enantioselectivity with a decrease in catalyst loading. A similar trend was observed with the reaction of chloromethyl 2-chlorophenyl ketone with the same *t*-Bu olefin, furnishing the product with the enantioselectivity of 82% ee. Reactions involving *t*-Bu chloromethyl ketone were sluggish and for the phenyl substituted Michael acceptor, the *cis*-cyclopropane was found to form as the major diastereomer, and for the *t*-Bu olefin, no reaction occurred.

In summary, cinchonidine was found to function as a Brønsted base catalyst in the reaction between β-substituted methylidenemalononitriles and chloromethyl ketones to furnish tetra-substituted cyclopropanes in up to 82% ee. Hydrogen-bonding seems to be essential for stereoinduction. In order to gain insights to the mechanism and improve the selectivity, other cinchona derivatives are also currently under investigation.

Acknowledgments

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15. Representative procedure (Table 2, entry 3): To a suspension of cinchonidine (1.1 mg, 3.7 μmol) and Na_2CO_3 (73.3 mg, 0.692 mmol) in dry toluene (1 mL) shielded from light was added a solution of phenylmethylidenemalononitrile (47.5 mg, 0.308 mmol) and α-chloroacetophenone (55.4 mg, 0.358 mmol) in toluene (2 mL) at 0 °C under N_2. After stirring at 0 °C for 5 d, the mixture was quenched with aq NH_4Cl. Usual workup followed by purification by PTLC (silica gel, hexane:EtOAc = 5:1) gave **8aa** as a white solid (61.6 mg, 0.226 mmol, 73%, 62% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, $J = 8.4$ Hz, 2H), 7.74 (t, $J = 7.6$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 2H), 7.49–7.43 (m, 3H), 7.41–7.38 (m, 2H), 4.04 (d, $J = 7.9$ Hz, 1H), 3.91 (d, $J = 8.0$ Hz, 1H).