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Dual Organocatalysis: Asymmetric Allylic–Allylic Alkylation of α,α-Dicyanoalkenes and Morita–Baylis–Hillman Carbonates

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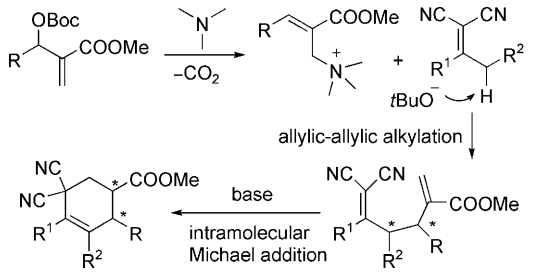
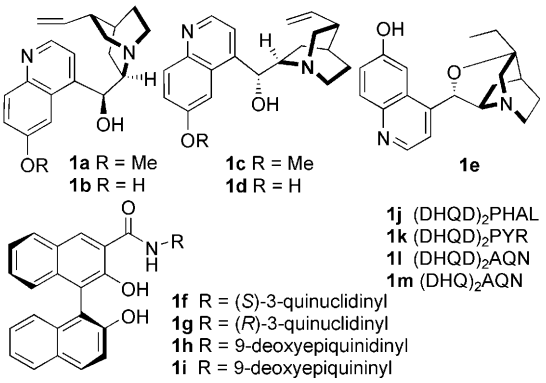
Asymmetric allylic alkylation (AAA) is a powerful protocol for accessing enantiomeric compounds that may find wide applications for further transformations. Previous work in this area has focused on the utilization of allylic alcohol derivatives as the electrophilic materials catalyzed by transition-metal complexes, and an array of interesting results has been presented over the past few decades.[1] Recently, another strategy, the allylic alkylation of Morita–Baylis–Hillman (MBH) adducts[2] with various nucleophiles by the metal-free catalysis of tertiary amines or phosphines,[3] has emerged as a very versatile approach to deliver multifunctional allylic-substituted compounds. High efficacy and excellent regioselectivities have been noted for a number of allylic alkylation reactions of MBH adducts; however, quite limited progress has been made in their asymmetric variants.[4] Therefore, the development of effective catalytic systems and new allylic alkylation reactions for MBH adducts is in high demand.

Recently, we and Jørgensen et al. independently established that α,α-dicyanoalkenes can perform as useful nucleophiles for an array of asymmetric allylic alkylation or functionalization reactions.[5] In our continuing efforts to expand the synthetic utility of these synthons, we envisaged that an unprecedented asymmetric allylic–allylic alkylation of α,α-dicyanoalkenes and MBH carbonates might be developed catalyzed by a suitable chiral tertiary amine. The counterparts from two reactants might further behave as Michael donor and acceptor, respectively, to furnish a tandem intramolecular conjugate addition;[6] thus chiral cyclohexenes with multiple substitutions could be efficiently constructed (Scheme 1). Furthermore, the resulting multifunctional alkylation products might also serve as versatile intermediates for other synthetic transformations.



Scheme 1. Proposed allylic–allylic alkylation and successive Michael addition for accessing chiral cyclohexenes with multiple substitutions.

The initial study with α,α-dicyanoalkene **2a** and MBH carbonate **3a** catalyzed by quinidine **1a** (Scheme 2, 10 mol%) was inspiring. The desired allylic–allylic alkyla-



Scheme 2. A variety of tertiary amine organocatalysts. $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PYR$ = hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether, $(DHQ)_2AQN$ = hydroquinine anthraquinone-1,4-diyl diether.

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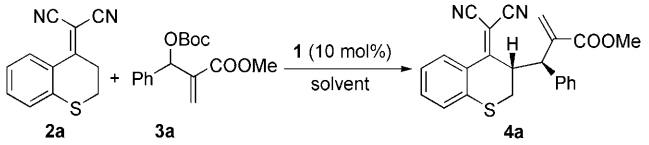
tion product **4a** was isolated as a single diastereomer, although the enantioselectivity was moderate (Table 1, entry 1). The domino intramolecular Michael addition product was not detected under the current catalytic conditions. Poorer results were obtained by catalysis by the 6′-demethylquinidine derivative **1b** (Table 1, entry 2). The reactions catalyzed by quinine **1c** and 6′-demethylquinine **1d** were also unsatisfactory (Table 1, entries 3 and 4).[7] Nevertheless, β-ICD **1e**, prepared from quinindine,[8] exhibited much higher catalytic activity, but the enantioselectivity was still modest (Table 1, entry 5). On the basis of the bifunctional characteristics of **1e**, catalyst **1f** containing (*S*)-BINOL ((*S*)-(−)-1,1′-bi-2-naphthol) and (*S*)-quinuclidine-3-amine structures was designed,[9] and better enantiocontrol was observed (Table 1, entry 6); however, catalyst **1g**, which contained (*S*)-BINOL and (*R*)-quinuclidine-3-amine, afforded a poor *ee* value (Table 1, entry 7). Unfortunately, the analogous catalysts **1h** and **1i** condensed from (*S*)-BINOL and 9-amino-9-deoxyepiquinidine and 9-amino-9-deoxyepiquinine,[10] respectively, showed no catalytic activity in the model reaction, probably for steric reasons (Table 1, entries 8 and 9). Subsequently, it was pleasing to find that commercially available modified cinchona alkaloid **1j** showed excellent enantioselectivity, but the reaction was too sluggish (Table 1, entry 10).[11] The presence of 10 mol% of (*S*)-BINOL as a Brønsted acid co-catalyst improved the isolated yield dramatically,[12,13] while long reaction times were still necessary (Table 1, entry 11). Gratifyingly, the reaction could be conducted at higher temperature in 1,2-dichloroethane (DCE) with little effect on the enantioselectivity (Table 1, entry 12). Moreover, other modified cinchona alkaloids such as **1k** and **1l** were tested, and even better catalytic efficacy was attained by the catalysis of $(DHQD)_2AQN$ (**1l**) (Table 1, entries 13 and 14). Finally, we obtained excellent results by employing two equivalents of the MBH adduct **3a** under the similar catalytic conditions (Table 1, entry 15, 95% yield, 97% *ee*, in 15 h).[4d] The same results were obtained when 10 mol% of (*R*)-BINOL was used (Table 1, entry 16). On the other hand, the enantiomer **4a**, opposite to that of **1l**, could be smoothly prepared in a good *ee* value in the presence of $(DHQ)_2AQN$ (**1m**), which was derived from dihydroquinine (Table 1, entry 17).

Table 1. Screening studies of organocatalytic allylic–allylic alkylation of α,α-dicyanoalkene **2a** and MBH carbonate **3a**.[a]

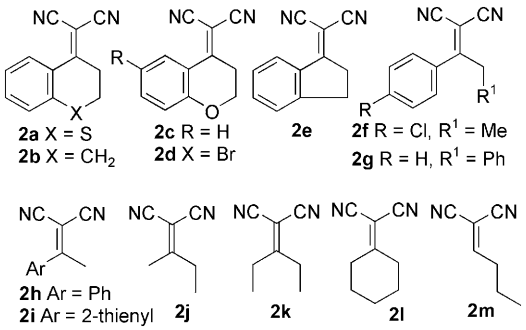


2a **3a** **4a**

Entry	Cat.	*T* [°C]	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	rt	DCM	84	51	66
2	**1b**	rt	DCM	120	82	33
3	**1c**	rt	DCM	72	54	−16
4	**1d**	rt	DCM	96	42	55
5	**1e**	rt	DCM	13	94	53
6	**1f**	rt	DCM	13	94	75
7	**1g**	rt	DCM	11	99	−17
8	**1h**	rt	DCM	24	–	–
9	**1i**	rt	DCM	24	–	–
10	**1j**	rt	DCM	168	28	95
11[d]	**1j**	rt	DCM	120	88	94
12[d]	**1j**	40	DCE	84	79	90
13[d]	**1k**	40	DCE	84	82	87
14[d]	**1l**	40	DCE	36	62	92
15[d,e]	**1l**	40	DCE	15	95	97
16[e,f]	**1l**	40	DCE	15	95	96
17[d,e]	**1m**	40	DCE	19	76	−86

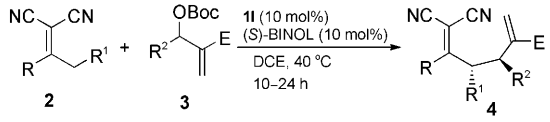
[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.1 mmol of **3a**, 0.01 mmol of **1** in 1 mL solvent. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis, d.r. > 99:1. [d] Adding 10 mol% of (*S*)-BINOL. [e] 0.2 mmol of **3a** was used. [f] Adding 10 mol% of (*R*)-BINOL.

Having established the optimal conditions, the scope of the novel allylic–allylic alkylation was explored with a variety of α,α-dicyanoalkenes **2** and MBH carbonates **3** (Scheme 3). In general excellent diastereoselectivities (d.r. > 99:1) were observed in the tested reactions. For α,α-dicyanoalkene **2a**, outstanding enantioselectivities were achieved with MBH carbonates bearing diversely substituted aryl or heteroaryl groups (Table 2, entries 1–11). MBH carbonates with strong electron-withdrawing substitutions exhibited higher reactivity, and better results were obtained at ambient temperature (Table 2, entries 5 and 6) or at 0°C (Table 2, entries 7 and 8).[14] Excellent results were achieved with the MBH adduct from methyl vinyl ketone (Table 2, entry 12). Nevertheless, a modest *ee* value was obtained for the MBH adduct from acrylonitrile even at 0°C (Table 2, entry 13). Subsequently, the reaction scope for α,α-dicyanoalkenes **2** was investigated. Remarkable enantioselectivities were obtained for α,α-dicyanoalkenes **2b**–**2d** and **2f**–**2i** derived from diversely structured cyclic or acyclic aryl ketones (Table 2, entries 14–21). It was noteworthy that the reaction could be conducted at much lower catalyst loadings. The same results were obtained in the reaction of **2b** and **3a** in the presence of only 2 mol% of **1l** and (*S*)-BINOL after 30 h (Table 2, entry 15). α,α-Dicyanoalkenes derived from aliphatic ketones also exhibited good reactivity in the allylic–allylic alkylation. Exclusive regioselectivity with excellent stereoselectivity was obtained at the methylene position for



Scheme 3. The structures of α,α-dicyanoalkenes **2**.

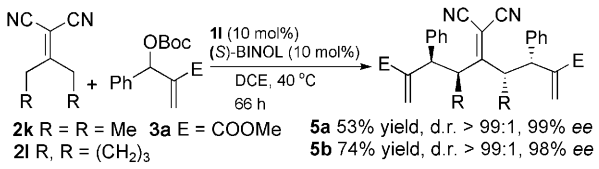
Table 2. Asymmetric allylic–allylic alkylation of α,α-dicyanoalkenes **2** and MBH carbonates **3**.[a]



Entry	2	R^2	E	Product	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	COOMe	**4a**	95	97[d]
2	**2a**	*p*-Cl-Ph	COOMe	**4b**	96	96
3	**2a**	*m*-Cl-Ph	COOMe	**4c**	95	96
4	**2a**	*o*-Cl-Ph	COOMe	**4d**	96	92
5[e]	**2a**	*p*-F-Ph	COOMe	**4e**	99	95
6[e]	**2a**	*m*-CN-Ph	COOMe	**4f**	94	90
7[f]	**2a**	*p*-NO_2-Ph	COOMe	**4g**	85	84
8[f]	**2a**	3,4-Cl_2-Ph	COOMe	**4h**	85	92
9	**2a**	*p*-MeO-Ph	COOMe	**4i**	93	93
10	**2a**	*m*-Me-Ph	COOMe	**4j**	85	96
11	**2a**	2-furyl	COOMe	**4k**	87	93
12	**2a**	Ph	$COCH_3$	**4l**	94	92
13[f]	**2a**	Ph	CN	**4m**	96	76
14	**2b**	Ph	COOMe	**4n**	82	96
15[g]	**2b**	Ph	COOMe	**4n**	85	96
16	**2c**	Ph	COOMe	**4o**	92	96
17	**2d**	Ph	COOMe	**4p**	92	97
18	**2f**	Ph	COOMe	**4q**	91	97
19	**2g**	Ph	COOMe	**4r**	79	97
20	**2h**	Ph	COOMe	**4s**	70	94
21	**2i**	Ph	COOMe	**4t**	73	95
22	**2j**	Ph	COOMe	**4u**	99	98
23[h]	**2a**	*p*-Cl-Ph	COOMe	**4b**	81	−80
24[h]	**2a**	*p*-MeO-Ph	COOMe	**4i**	85	−80

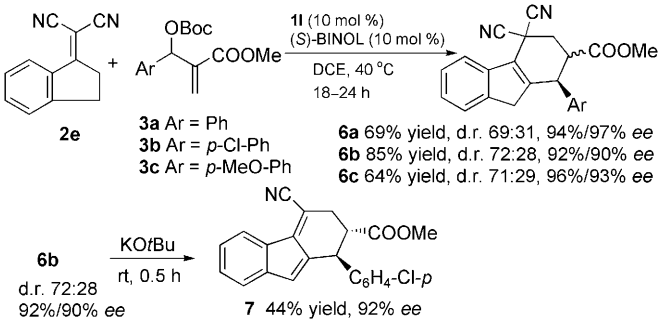
[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2**, 0.2 mmol of **3**, 10 mol% of **1l** and 10 mol% of (*S*)-BINOL in 1.0 mL DCE at 40°C for 10–24 h. [b] Yield of isolated product. [c] Based on chiral HPLC analysis, d.r. > 99:1. [d] The absolute configuration of **4a** was determined by X-ray analysis, please see Supporting Information.[15] The other products were assigned by analogy. [e] At room temperature. [f] At 0°C for 65 h. [g] With 2 mol% of **1l** and (*S*)-BINOL at 0.5 mmol scale, for 30 h. [h] With **1m** as the catalyst.

the unsymmetrical substrate **2j** (Table 2, entry 22). Mixtures of mono- and double-allylic alkylation products were formed when symmetric α,α-dicyanoalkenes **2k** and **2l** were applied; nevertheless, the double-allylic alkylation adducts **5a** and **5b** with four stereogenic centers could be isolated as single diastereomers with remarkable *ee* values by employing four equivalents of the MBH carbonate **3a** (Scheme 4). Nevertheless, α,α-dicyanoalkene **2m**, which was derived from the aliphatic aldehyde, could not be successfully applied in this allylic–allylic alkylation, and the self-condensation of **2m** was observed by the catalysis of basic **1l**. On the other hand, the opposite enantiomeric allylic–allylic products **4b** and **4i** were also prepared in good *ee* values catalyzed by **1m** under similar conditions (Table 2, entries 23 and 24).



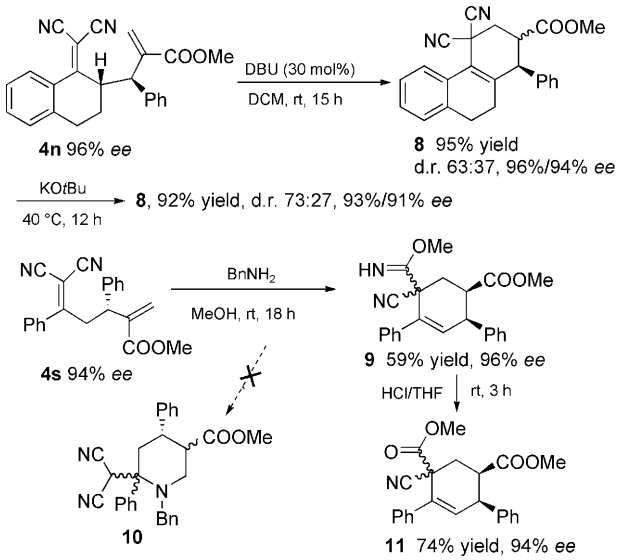
Scheme 4. Double allylic–allylic alkylation of symmetric α,α-dicyanoalkenes **2k** and **2l**.

Interestingly, under the same catalytic conditions as above, for α,α-dicyanoalkene **2e**, cyclohexene derivatives **6a–6c** were directly isolated in excellent enantioselectivities with modest d.r. ratios. Apparently, the expected allylic–allylic alkylation happened, followed by a domino intramolecular Michael reaction, which generated the desired cyclohexene products. The final protonation process gave rise to unsatisfactory diastereoselectivity. The elimination of HCN was observed when the mixture of **6b** was treated with KO*t*Bu, from which the diastereomerically pure diene **7** could be separated (Scheme 5).



Scheme 5. A domino process for accessing cyclohexene derivatives.

Likewise, the allylic–allylic alkylation product **4n** could be also cyclized to give the desired cyclohexene **8** in the presence of the stronger organic base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) without racemization. Nevertheless, the same product **8** was recovered after treating with KO*t*Bu (Scheme 6). On the other hand, an unexpected cyclic product **9** was afforded when the allylic compound **4s**



Scheme 6. Transformations of allylic adducts.

was allowed to react with $BnNH_2$ in MeOH, rather than the formal double Michael adduct **10**. The chiral cyano ester **11** was smoothly prepared by the hydrolysis of intermediate **9** (Scheme 6).[16]

In conclusion, we have developed the first highly enantioselective allylic–allylic alkylation of α,α-dicyanoalkenes and Morita–Baylis–Hillman carbonates by dual organocatalysis of commercially available modified cinchona alkaloids and (*S*)-BINOL. Excellent stereoselectivities were achieved for a broad spectrum of substrates (d.r. > 99:1, up to 99% *ee*). Several enantioenriched compounds with complex cyclic structures were derived from the allylic products.[17] We believe that this catalytic strategy will be applicable to other asymmetric reactions of MBH adducts and further work in this direction is currently underway.

Acknowledgements

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Keywords: asymmetric allylic alkylation · cyclohexenes · dicyanoalkenes · organocatalysis · Morita–Baylis–Hillman carbonates

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[13] For more results of Brønsted acid co-catalyst screening, see the Supporting Information.

[14] MBH carbonates derived from aliphatic aldehydes exhibit much lower reactivity toward **2a** under the current catalytic system and require further exploration.

[15] CCDC-712759 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[16] The relative configuration of the quaternary carbon atom of compound **11** has not been assigned yet, see the Supporting Information.

[17] For an excellent review on the Morita–Baylis–Hillman reaction assisted synthesis of cyclic frameworks, see: V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511–4574.

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