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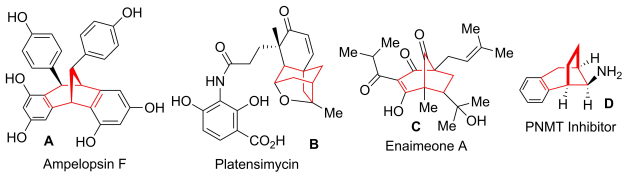
Organocatalytic Asymmetric Formal [3+2]-Cycloaddition as a Versatile Platform to Methanobenzo[7]annulenes**

Dhevalapally B. Ramachary, Mohammed Anif Pasha,[b] and Guguloth Thirupathi[b]*

***Abstract**: Pharmaceutically and structurally important methanobenzo[7]annulenes were synthesized in very good yields with excellent enantio- and diastereoselectivities through an unprecedented competitive organocatalytic formal [3+2]-cycloaddition from the readily available 2-alkyl-3-hydroxynaphthalene-1,4-diones and alkyl vinyl ketones.*

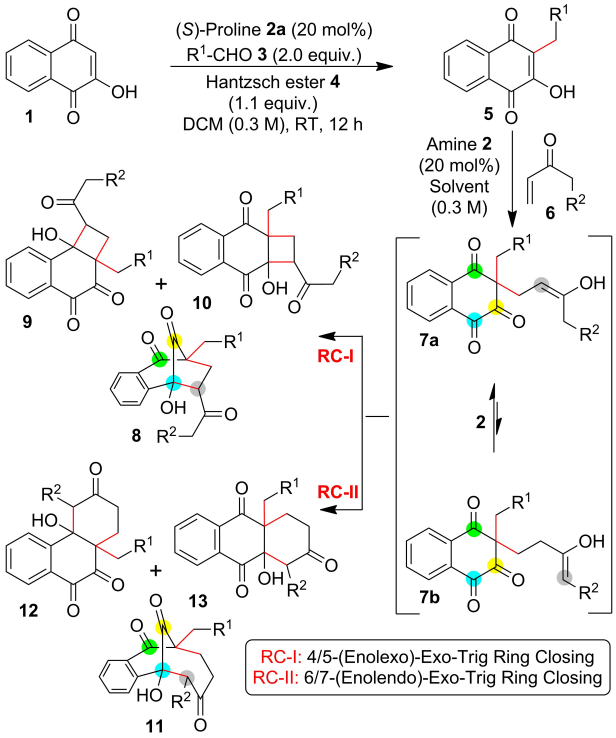
Bicyclo[3.2.1]octane unit is widely present in both natural and synthetic compounds which possess various biological activities (Scheme 1).[1] To date chiral bicyclo[3.2.1]octanes have been known to be prepared,[2] using organocatalytic Michael–aldol, Michael–Henry, Michael-isomerization-Michael, and Michael–elimination–Michael cascades from simple β-keto esters or ketones with α,β-unsaturated aldehydes or nitrostyrenes, respectively. Nevertheless, we still need newer high yielding catalytic methods for creating methanobenzo[7]annulenes containing multiple chiral centers, in a stereocontrolled fashion.[3]



Scheme 1. Biologically active bicyclo[3.2.1]octanes.

We have developed here for the first time an economic metal-free approach for the high-yielding stereoselective synthesis of privileged bicyclo[3.2.1]octanes as substituted methanobenzo[7]annulenes in both achiral and chiral forms, through a novel organocatalytic formal [3+2]-cycloaddition [or] domino Michael/*5-(enolexo)-exo-trig* cyclization reactions of laboratory prepared 2-alkyl-3-hydroxynaphthalene-1,4-diones with commercially available alkyl vinyl ketones under catalytic and ambient conditions.

Hence, synthesis and investigation of synergistic nucleophilic and electrophilic nature of 2-alkyl-3-hydroxynaphthalene-1,4-diones **5** through organocatalysis presents an intriguing synthetic challenge to work on. Starting materials, 2-alkyl-3-hydroxynaphthalene-1,4-diones **5** could be prepared in good yields by using recently emerging organocatalytic three-component reductive alkylation (TCRA) or reductive coupling reaction.[4-6] Surprisingly, there is no asymmetric transformation known utilizing 2-alkyl-3-hydroxynaphthalene-1,4-diones **5**[7] and herein, we used them as suitable starting materials along with alkyl vinyl ketones **6** for the designed asymmetric domino Michael and *5-(enolexo)-exo-trig* cyclizations or formal [3+2]-cycloadditions (Scheme 2).[8]



Scheme 2. Reaction layout for the methanobenzo[7]annulenes through domino Michael and *5-(enolexo)-exo-trig* cyclizations or formal [3+2]-cycloadditions.

Building on this backdrop and also due to the ease with which TCRA products could be made efficiently, we surmised to utilize L-proline **2a** would catalyze the TCRA reaction of Lawsone **1**,

[*] Prof. Dr. D. B. Ramachary, Md. Anif Pasha, and Dr. G. Thirupathi
Catalysis Laboratory, School of Chemistry
University of Hyderabad
Hyderabad-500 046 (India)
Fax: +91-40-23012460
E-mail: ramsc@uohyd.ac.in and ramchary.db@gmail.com
Homepage: http://chemistry.uohyd.ac.in/~dbr/index.htm

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[b] MAP and GT both are contributed equally to this work.

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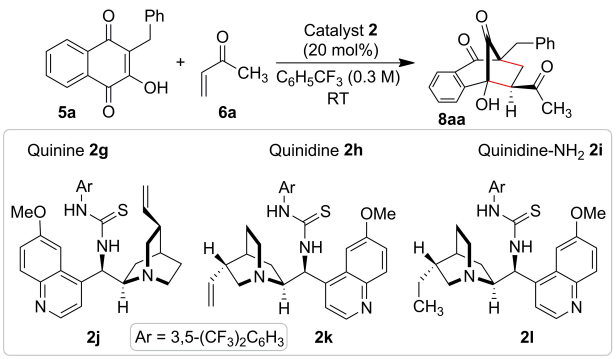
aldehydes **3** and Hantzsch ester **4** to furnish the alkylation products **5** in very good yields (Scheme 2). Organocatalytic domino Michael-aldol reactions between the resulting 2-alkyl-3-hydroxynaphthalene-1,4-diones **5** with alkyl vinyl ketones **6** would yield the unexpected methanobenzo[7]annulenes **8** in a highly stereoselective and product specific manner over competition with five other ring closing cyclizations (Scheme 2). To understand the designed domino reaction rate, catalyst/solvent effect, selectivity, and product distribution over other possible ring closing cyclizations, first we investigated the organocatalytic racemic *5-(enolexo)-exo-trig* cyclization through domino Michael-aldol reactions between hydroxy-dione **5a** and methyl vinyl ketone **6a** under the catalysis of achiral amines/base **2b-f** (Table S1, see SI). After thorough investigation, we found that DMAP **2c** would catalyse the racemic domino reaction of **5a** with **6a** in toluene at 25 °C for 9 h to furnish the achiral methanobenzo[7]annulene **8aa** in 93% yield with 4:1 *dr* (Table S1, see SI for full details).

Table 1. Investigation of the proposed asymmetric reaction.[a]



Entry	Catalyst **2** [20 mol-%]	Time [h]	Yield [%][b] **8aa**	dr [%][c] **8aa**	ee [%][d] **8aa**
1[e]	**2a**	20	90	1:1	7 [0]
2[e]	**2g**	36	90	5:1	34 [23]
3[e]	**2h**	36	90	6:1	42 [28]
4[e]	**2i**	32	80	2:1	0 [0]
5[e, f]	**2j**	24	90	86:1	90 [85]
6[f]	**2j**	72	75	24:1	94 [85]
7	**2j**	8	86	22:1	91 [86]
8[f,g]	**2j**	72	73	22:1	91 [94]
9[h]	**2k**	6	90	61:1	95 [99]
10[f]	**2k**	21	85	99:1	97 [99]
11[h,i]	**2k**	11	87	66:1	93 [99]
12[h,j]	**2k**	6	90	46:1	95 [99]
13[h]	**2l**	7	80	9:1	94 [99]

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **6a** relative to the **5a** (0.3 mmol) in the presence of 20-mol% of catalyst **2**. [b] Yield refers to the column-purified product. [c] dr determined by CSP HPLC analysis. [d] ee determined by CSP HPLC analysis and values in paranthesis represent for minor diastereomer. [e] Toluene as the solvent. [f] T = 0-3 °C. [g] C_6F_6 as the solvent. [h] T = 20 °C. [i] 15 mol% of **2k** used. [j] 30 mol% of **2k** used. Note: Entries 5-8 represents the opposite enantiomers of compound **8aa**.

Next we focused to investigate the asymmetric induction in the designed domino reaction (Table 1). Stimulating investigative reports on the cinchona alkaloid catalysis,[9] by Deng and other research groups inspired us to utilize them in our present studies (Table 1). To start with, simple amino acid *L*-proline **2a** was tested as the catalyst for the chiral version of the domino reaction of **5a** with **6a** in toluene at 25 °C for 20 h (Table 1, entry 1). Though the reaction progressed well to furnish the desired product **8aa** in very good yield, the selectivity obtained was disappointingly poor. The same reaction with quinine **2g** as the catalyst at 25 °C for 36 h furnished the chiral product **8aa** in 90% yield with 34% *ee* and 5:1 *dr* (Table 1, entry 2). Quinidine **2h**-catalysis also furnished the product **8aa** with little improvement (90% yield, 42% *ee* and 6:1 *dr*, entry 3). Surprisingly, the same reaction under the catalysis of *epi*-quinidine-NH_2 **2i** at 25 °C for 32 h furnished the product **8aa** in 80% yield with 0% *ee* and 2:1 *dr* (Table 1, entry 4).

After understanding the reactivity pattern of quinine/quinidine with **5a** and **6a**, we realized that the *tert*-amine of **2g-h** is acting as base to induce the nucleophilic nature of **5a** through hydrogen bonding, but the facial selectivity and electrophilicity of **6a** are not induced much under the reaction conditions. To perform the synergistic activation of both the functional groups of **5a** and **6a**, we thought of using the primary amine-thiourea **2j**, **2k** or **2l** as the catalyst to achieve high selectivity. Interestingly, the domino reaction of **5a** and **6a** with 20 mol% of 9-epi-aminoquinidine-thiourea **2j** in toluene at 0-3 °C for 24 h furnished the chiral product (+)-**8aa** in 90% yield with 90% *ee* and 86:1 *dr* as expected (Table 1, entry 5). The same reaction in trifluorotoluene at 0-3 °C for longer time (72 h) furnished the chiral product (+)-**8aa** in reduced (75%) yield with increased (94%) *ee* and decreased (24:1) *dr*; but same reaction at 25 °C furnished (+)-**8aa** in 86% yield with 91% *ee* and 22:1 *dr* within 8 h (Table 1, entries 6-7). There is not much improvement in hexafluorobenzene as solvent compared to trifluorotoluene (entry 8). During subsequent optimization studies, we obtained the antipode (−)-**8aa** in 85-90% yield with high enantio- and diastereoselectivities (up to 97% *ee* and 99:1 *dr*) under the catalysis of 9-epi-aminoquinine-thiourea **2k** (15-30 mol%) in trifluorotoluene at 0-3 or 20 °C for 6-21 h (Table 1, entries 9-12). From these studies, the final optimized condition for the asymmetric domino cyclization between **5a** and **6a** was established to be **2k**-catalysis in trifluorotoluene at 20 °C for 6 h and generated the chiral (−)-**8aa** in 90% yield with 95% *ee* and 61:1 *dr* (Table 1, entry 9). Not much improvement observed under the catalysis of 9-epi-aminodihydroquinine-thiourea **2l** compared to **2k** (Table 1, entry 13).

Further, the scope of the 9-epi-aminoquinine-thiourea **2k**-catalyzed domino Michael/*5-(enolexo)-exo-trig* cyclization was showcased by synthesising a library of functionalized chiral methanobenzo[7]annulenes **8ba-ua** from the reaction between various 2-alkyl-3-hydroxynaphthalene-1,4-diones **5b-u** and methyl vinyl ketone **6a** (Table 2). Various hydroxy-diones **5b-u** used in this reaction were synthesized in very good yields by using organocatalytic TCRA or reductive coupling of Lawsone **1**, aldehydes **3b-u** and Hantzsch ester **4** as shown in Eq.S1 and Table S2 (see SI for full details). The domino reaction was capable of generating the chiral methanobenzo[7]annulenes **8ba-ua** bearing a variety of functional groups such as neutral, electron-donating, electron-withdrawing, hetero-atom substituted and halogenated, with excellent *ee*'s (up to 99% *ee*) and *dr*'s (up to 45:1 *dr*) in very good yields (Table 2). Thus for the first time, a variety of unchanged hydroxy-diones **5b-u** were used as source of *in situ* generated chiral enolates and utilized as mild nucleophiles in a domino reaction in order to furnish the functionalized drug-like methanobenzo[7]annulenes **8ba-ua**.

Table 2. 2-Alkyl-3-hydroxynaphthalene-1,4-dione scope.[a]

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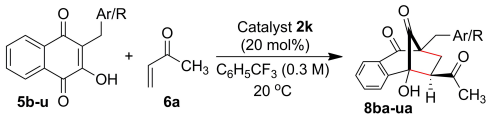
[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **6a**

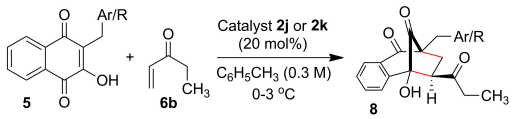


Entry	Ar/R **5**	*t* [h]	Yield **8** [%][b]	dr[c]	*ee* [%][d]
1	**5b**: Ar = 4-FC_6H_4	8	80 (**8ba**)	20:1	95 [99]
2	**5c**: Ar = 4-ClC_6H_4	10	90 (**8ca**)	18:1	95 [99]
3	**5d**: Ar = 4-BrC_6H_4	13	96 (**8da**)	36:1	96 [99]
4	**5e**: Ar = 4-$CH_3C_6H_4$	11	88 (**8ea**)	22:1	99 [84]
5	**5f**: Ar = 4-$OMeC_6H_4$	8	95 (**8fa**)	23:1	92 [99]
6	**5g**: Ar = 4-$CF_3C_6H_4$	22	70 (**8ga**)	11:1	93 [89]
7	**5h**: Ar = 4-CNC_6H_4	22	65 (**8ha**)	9:1	95 [95]
8	**5i**: Ar = 2-FC_6H_4	3	75 (**8ia**)	9:1	90 [88]
9[e]	**5j**: Ar = 2-BrC_6H_4	36	70 (**8ja**)	6:1	88 [98]
10[e]	**5k**: Ar = 2-$CH_3C_6H_4$	15	75 (**8ka**)	5:1	82 [81]
11[e]	**5l**: Ar = 2-$N_3C_6H_4$	16	75 (**8la**)	2.7:1	90 [88]
12[e]	**5m**: Ar = 1-Naphthyl	36	75 (**8ma**)	2.0:1	82 [86]
13	**5n**: Ar = 2-Furyl	9	78 (**8na**)	11:1	93 [86]
14	**5o**: Ar = 2-Thiophenyl	5	70 (**8oa**)	10:1	92 [81]
15	**5p**: Ar = *N*-Boc-indole-3-yl	8	91 (**8pa**)	16:1	84 [82]
16	**5q**: R = CH_3	2	90 (**8qa**)	28:1	96 [92]
17	**5r**: R = $CH_2CH_2CH_2CH_3$	6	95 (**8ra**)	22:1	94 [99]
18	**5s**: R = CH_2CHMe_2	6	99 (**8sa**)	24:1	94 [84]
19	**5t**: R = $CH_2[CH_2]_5CH_3$	6	95 (**8ta**)	12:1	95 [99]
20	**5u**: R = CH_2CH_2Ph	6	95 (**8ua**)	45:1	90 [99]

relative to the **5b-u** (0.3 mmol) in the presence of 20-mol% of catalyst **2k**. [b] Yield refers to the column-purified product. [c] dr determined by CSP HPLC analysis. [d] ee determined by CSP HPLC analysis and values in paranthesis represent for minor diastereomer. [e] Reaction performed at 40 °C.

Interestingly, the domino reaction of **6a** with 4-halobenzyl, 4-methylbenzyl, and 4-methoxybenzyl substituted hydroxy-diones **5b-f** under the catalysis of **2k** at 20 °C for 8-13 h furnished the chiral products (–)-**8ba** to (–)-**8fa** in 80-96% yields with 92-99% *ee* and 18:1-36:1 *dr* (Table 2, entries 1-5). Likewise, the domino reaction of hydroxy-diones **5g-h** containing 4-(trifluoromethyl)benzyl and 4-cyanobenzyl with **6a** under the **2k**-catalysis at 20 °C for 22 h furnished the expected chiral products (–)-**8ga** and (–)-**8ha** in good yields (70%, 65%) with high (93%, 95%) *ee* and moderate (11:1, 9:1) *dr* respectively (Table 2, entries 6-7). Further, the domino reaction of hydroxy-diones **5i-m** containing 2-fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-azidobenzyl and naphthalen-1-ylmethyl with **6a** under the **2k**-catalysis at 40 °C for 3-36 h furnished the chiral products (–)-**8ia** to (–)-**8ma** in good (70-75) yields and (82-90%) *ee's* with moderate to poor (2.0:1 to 9:1) *dr's*. Notably, the same reactions didn't do well at 20 °C even for longer reaction times, except in the case of **5i**, may be due to the *ortho*-substitution effect (Table 2, entries 8-12). Hetero-atom substituted hydroxy-diones **5n-p** too partook in the domino reaction with **6a** under the catalysis of **2k** at 20 °C for 5-9 h furnished the chiral products (+)-**8na** to (–)-**8pa** in 70-91% yields with 84-93% *ee* and 10:1-16:1 *dr* (Table 2, entries 13-15). Correspondingly, the hydroxy-diones **5q-u** containing five different alkyl groups also involved in the domino reaction with **6a** under the **2k**-catalysis at 20 °C for 2-6 h to furnish the chiral products (+)-**8qa** to (–)-**8ua** in very good (90-99) yields and (90-96%) *ee's* with good to excellent (12:1 to 45:1) *dr's* (Table 2, entries 16-20). All these results put together point out conclusively that the strength of the hydrogen-bonding between the hydroxy-diones **5b-u** possessing 2-alkyl substitution and the catalyst 9-epi-aminoquinine-thiourea **2k** dictates the result of the reaction rate and selectivity. We established the structure of the domino products **8** by NMR analysis and absolute stereochemistry finally confirmed by X-ray structure analysis on (–)-**8da** and (–)-**8ea** (Figures S1 and S2, see the SI).[10]

Table 3. Alkyl vinyl ketone scope.[a]

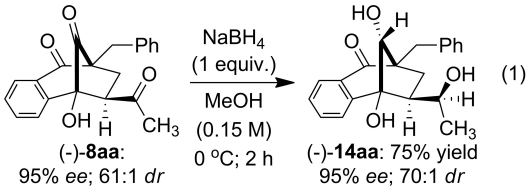


Entry	Ar/R **5**	Cat. **2**	*t* [h]	Yield **8** [%][b]	dr[c]	*ee* [%][d]
1[e]	**5a**: Ar = C_6H_5	**2j**	13	80 (**8ab**)	90:1	74 [–]
2[e]	**5a**: Ar = C_6H_5	**2k**	13	80 (**8ab**)	25:1	76 [99]
3	**5a**: Ar = C_6H_5	**2j**	48	85 (**8ab**)	53:1	81 [89]
4	**5a**: Ar = C_6H_5	**2k**	72	85 (**8ab**)	14:1	83 [99]
5	**5b**: Ar = 4-FC_6H_4	**2j**	48	65 (**8bb**)	90:1	97 [–]
6	**5c**: Ar = 4-ClC_6H_4	**2j**	48	75 (**8cb**)	90:1	73 [99]
7	**5e**: Ar = 4-$CH_3C_6H_4$	**2j**	72	65 (**8eb**)	16:1	74 [74]
8	**5f**: Ar = 4-$OMeC_6H_4$	**2j**	72	80 (**8fb**)	84:1	87 [38]
9	**5q**: R = CH_3	**2j**	24	90 (**8qb**)	11:1	74 [90]
10	**5t**: R = $CH_2[CH_2]_5CH_3$	**2j**	48	90 (**8tb**)	89:1	79 [61]
11	**5u**: R = CH_2CH_2Ph	**2j**	48	90 (**8ub**)	22:1	64 [79]
12	**5c**: Ar = 4-ClC_6H_4	**2k**	26	88 (**8cb**)	67:1	80 [99]
13	**5e**: Ar = 4-$CH_3C_6H_4$	**2k**	35	65 (**8eb**)	11:1	80 [87]
14	**5f**: Ar = 4-$OMeC_6H_4$	**2k**	48	87 (**8fb**)	62:1	98 [99]
15	**5n**: Ar = 2-Furyl	**2k**	72	75 (**8nb**)	97:1	84 [99]
16	**5q**: R = CH_3	**2k**	35	75 (**8qb**)	9:1	77 [74]
17	**5t**: R = $CH_2[CH_2]_5CH_3$	**2k**	24	95 (**8tb**)	10:1	86 [86]
18	**5u**: R = CH_2CH_2Ph	**2k**	26	92 (**8ub**)	7:1	84 [85]
19[e,f]	**5a**: Ar = C_6H_5	**2k**	12	80 (**8ac**)	76:1	79 [96]
20[g]	**5a**: Ar = C_6H_5	**2k**	22	80 (**8ad**)	28:1	76 [87]
21[g]	**5a**: Ar = C_6H_5	**2k**	5.5	90 (**8ae**)	97:1	22 [99]

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv. of **6b-e** relative to the **5a-u** (0.3 mmol) in the presence of 20-mol% of catalyst **2j** or **2k**. [b] Yield refers to the column-purified product. [c] dr determined by CSP HPLC analysis. [d] ee determined by CSP HPLC analysis and values in paranthesis represent for minor diastereomer. [e] Reaction performed in $C_6H_5CF_3$ at 40 °C. [f] *n*-Propyl vinyl ketone **6c** used. [g] Benzyl vinyl ketone **6d** or phenyl vinyl ketone **6e** used in $C_6H_5CF_3$ at 20 °C. Note: Entries 1, 3, 5-11 represents the opposite enantiomers of compound **8**.

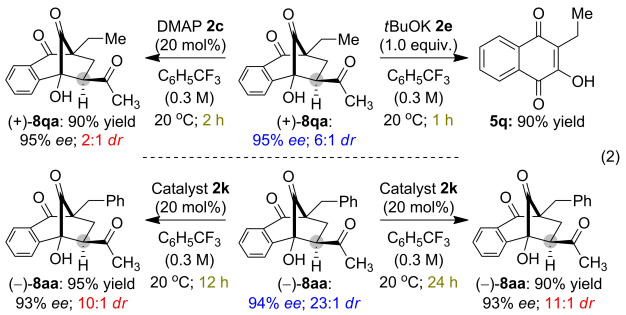
Moreover, the scope of **2j** or **2k**-catalyzed domino reaction was extended further by developing a library of optically pure methanobenzo[7]annulenes **8ab-ae** through the reaction of various hydroxy-diones **5a-u** with different alkyl vinyl ketones **6b-e** (Table 3). Notably, the domino reaction of ethyl vinyl ketone **6b** with hydroxy-dione **5a** under the catalysis of **2j** or **2k** in trifluorotoluene at 0-3 or 20 °C for 72 h furnished the chiral product **8ab** in very poor conversions; but the same reaction at 40 °C for 13 h furnished the chiral product (+)-**8ab** in 80% yield with 74% *ee* and 90:1 *dr* and (–)-**8ab** in 80% yield with 76% *ee* and 25:1 *dr* respectively (Table 3, entries 1-2). Also, the same reaction under **2j**-catalysis in toluene at 0-3 °C for 48 h furnished the chiral product (+)-**8ab** in 85% yield with 81% *ee* and 53:1 *dr* and under the **2k**-catalysis in toluene at 0-3 °C for 72 h furnished (–)-**8ab** in 85% yield with 83% *ee* and 14:1 *dr* respectively (Table 3, entries 3-4). In a similar

manner, domino reaction of hydroxy-diones **5b-u** containing 4-fluorobenzyl, 4-chlorobenzyl, 4-methylbenzyl, 4-methoxybenzyl, ethyl, *n*-octyl and 3-phenylpropyl with ethyl vinyl ketone **6b** under the **2j**-catalysis in toluene at 0-3 °C for 24-72 h furnished the chiral products (+)-**8bb** to (+)-**8ub** in good to excellent (65-90) yields, (64-97%) *ee's* and (11:1 to 90:1) *dr's* (Table 3, entries 5-11). Interestingly, the same reactions under the **2k**-catalysis in toluene at 0-3 °C furnished the opposite enantiomers of (−)-**8cb** to (−)-**8ub** in improved yields (65-95) and *ee's* (77-98%) but with reduced (7:1 to 97:1) *dr's* (Table 3, entries 12-18). Reaction of hydroxy-dione **5a** with *n*-propyl vinyl ketone **6c** under the **2k**-catalysis at 40 °C for 12 h furnished the chiral product (−)-**8ac** in 80% yield and 79% *ee* with 76:1 *dr* (Table 3, entry 19). Reaction of **5a** with benzyl vinyl ketone **6d** under the **2k**-catalysis at 20 °C for 22 h furnished the chiral product (−)-**8ad** in 80% yield with 76% *ee* and 28:1 *dr* (Table 3, entry 20). Surprisingly, domino reaction of **5a** with phenyl vinyl ketone **6e** under the **2k**-catalysis in trifluorotoluene at 20 °C for 5.5 h furnished the expected product **8ae** in 90% yield with poor (22%) *ee* and high (97:1) *dr* (Table 3, entry 21). In similar conditions, we didn't observe the domino reaction between **5a** and 3-methylbut-3-en-2-one **6f** or ethyl acrylate **6g** for even for longer reaction times [results not shown in Table 3]. It is evident from the results that the size of the alkyl group on the enone **6** controls the reaction rate and selectivity.



(1)

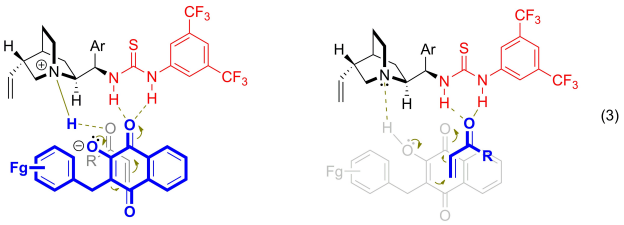
In line with synthetic applications, the generated triones **8** were utilized for the synthesis of hydroxy-rich chiral compounds **14** by simple reduction (Eq. 1). Straightforward $NaBH_4$ (1.0 equiv.) reduction of the chiral methanobenzo[7]annulene (−)-**8aa** in dry CH_3OH at 0 °C for 2 h produced the trihydroxy compound (−)-**14aa** in 75% yield with 95% *ee* and 70:1 *dr* (Eq. 1). Basic nature of the catalyst **2** has strong influence on the stability and selectivity of the chiral products **8** (Eq. 2). Treatment of (+)-**8qa** with 20 mol-% DMAP **2c** at 20 °C for 2 h resulted the product (+)-**8qa** with reduced *dr* and same *ee*; but treatment with one equivalent of KO^{t}Bu **2e** at 20 °C for 1 h gave completely the starting materials **5q** and **6a** in 90% yield through *retro*-aldol/aldol and *retro*-aldol/*retro*-Michael reactions, respectively (Eq. 2). In a similar manner, reaction of (−)-**8aa** with 20 mol-% 9-epi-aminoquinine-thiourea **2k** at 20 °C for 12-24 h resulted the (−)-**8aa** with reduced *dr* and almost same *ee*; which



(2)

is strong supportive of stepwise mechanism rather than concerted in the designed domino reactions (Eq. 2).

Despite the fact that further studies are necessary for elucidating the mechanism of the stereoselective domino Michael/*5-(enolexo)-exo-trig* cyclization through **2j**- or **2k**-catalysis, most probably, the reaction might be proceeding in a stepwise fashion between the *in situ* generated *3-alkyl-1,4-dioxo-1,4-dihydronaphthalen-2-olate* and alkyl vinyl ketones **6** (Eq. 3). The experiential high stereoselectivity could be explained on account of X-ray crystal structure studies, through an allowed pre-transition state, where the *si*-face of alkyl vinyl ketone **6** approaches the *re*-face of the *in situ* generated *3-alkyl-1,4-dioxo-1,4-dihydronaphthalen-2-olate* owing to the strong hydrogen-bonding, electrostatic attraction and less steric hindrance between the catalyst **2k** and substrates **5/6** as shown in the **TS-1**. The model **TS-2** having weak hydrogen-bonding interactions between the catalyst **2k** and substrates **5/6** might explain the generation of the minor enantiomer (Eq. 3). We have also got strong support to our hypothesis of involving stable pre-transition state (*pre*-**TS-1**) through careful investigation of the domino reaction of **5g** with **6a** or **6b** under the **2k**-catalysis using electrospray ionization with high resolution mass spectrometry (ESI-HRMS) technique, which enabled us to identify critical proposed *pre*-**TS-1** or Michael adduct-catalyst complex (Figure S3-S6, see SI). The ESI-HRMS spectrum of an on-going reaction of **5g** with **6a** or **6b** (3 equiv.) in the presence of **2k** (20 mol-%) in the trifluorotoluene at 0-3 °C reveals the formation of the key catalytic intermediate *pre*-**TS-1**·Na^+ (*m/z* 1019.2865) or *pre*-**TS-1**·Na^+ (*m/z* 1033.3021) respectively. One of the important innovation in these reactions is that, out of the three carbonyls existed in the key Michael adduct intermediate (**7a**, Scheme-2), only C1-carbonyl group involved as the electrophile in the subsequent aldol reaction may be due to the consideration of length of the side chain *enolexo* and also structural/electronic nature of *in situ* generated *naphthalene-1,2,4(3H)-trione*. Even though, according to preliminary ab-initio calculations, the charge on the C1 carbon is least (C4 = 0.397096; C2 = 0.406116; C1 = 0.349861).



(3)

In conclusion, for the first time, we have utilized the *in situ* generated chiral enolates from lab-made 2-alkyl-3-hydroxynaphthalene-1,4-diones by 9-epi-aminoquinine-thiourea catalysis, as suitable dipolarophiles for formal [3+2]-cycloaddition with alkyl vinyl ketones to furnish the highly functionalized chiral methanobenzo[7]annulenes as a single compound out of six in very good yields with high *ee*'s/*dr*'s. A library of methanobenzo[7]annulenes in both achiral and chiral forms were generated, which would be applicable in natural and pharmaceutical chemistry. Further work in this line of exploring the potential of novel modes available for the perfect pair of chiral amines with unmodified 2-alkyl-3-hydroxynaphthalene-1,4-diones is in progress.

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[10] CCDC-1555167 [(−)-**8da**] and CCDC-1555168 [(−)-**8ea**] contains the supplementary crystallographic data for this paper.

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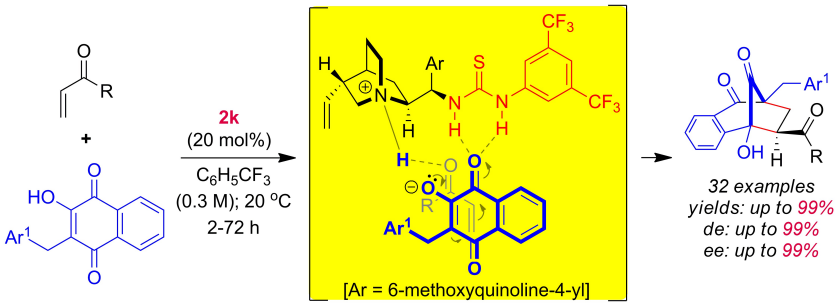
Angewandte Communications

Entry for the Table of Contents

Methanobenzo[7]annulenes

D. B. Ramachary,* Md. Anif Pasha, and G. Thirupathi __**Page – Page**

Organocatalytic Asymmetric Formal [3+2]-Cycloaddition as a Versatile Platform to Methanobenzo[7]annulenes



Easy and efficient clicking to chiral methanobenzo[7]annulenes: An unprecedented organocatalytic asymmetric domino Michael/*5-(enolexo)-exo-trig* cyclization or formal [3+2]-cycloaddition of 2-alkyl-3-hydroxynaphthalene-1,4-dione–alkyl vinyl ketone is reported. It is an efficient, first catalytic asymmetric intermolecular domino reaction of lawsone derivatives with alkyl vinyl ketones.