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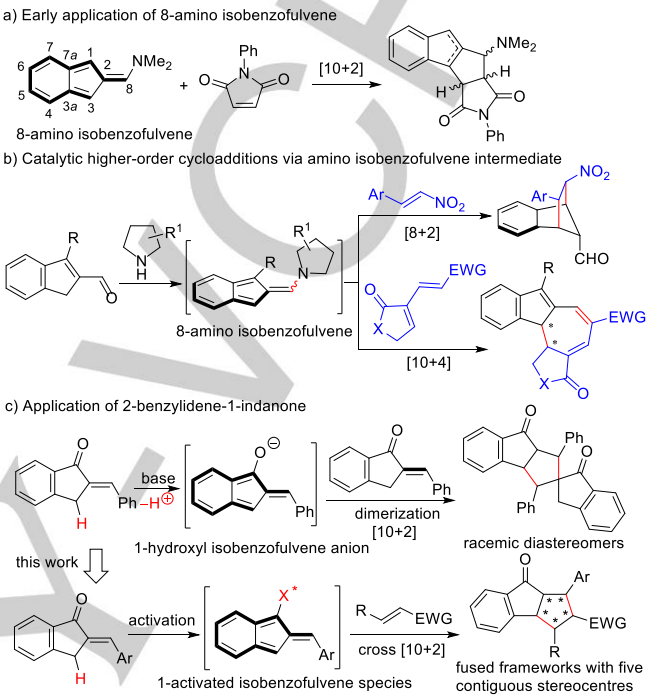
Asymmetric Cross [10+2] Cycloaddtions of 2-Alkylidene-1-indanones and Activated Alkenes under Phase-Transfer Catalysis

Yang Yang,[a] Ying Jiang,[a] Wei Du,[a] and Ying-Chun Chen*[a,b]

Abstract: The isobenzofulvene species are versatile synthons in organic chemistry, which have been employed in diverse challenging higher-order cycloaddition reactions. Here, the first chemoselective and asymmetric cross [10+2] cycloaddtion reaction between activated 2-alkylidene-1-indanones and a variety of electron-deficient alkenes has been developed, relying on the in situ generation of dearomative 1-hydroxyl isobenzofulvene anion intermediates under the catalysis of a newly designed bulky cinchona-derived phase transfer substance. An array of fused frameworks with multifunctionalities were generally furnished in excellent diastereo- and enantioselectivity, even at 1 mol% catalyst loadings.

The cycloaddition reaction is a highly efficient and atom-economical protocol that can construct cyclic compounds containing multiple stereogenic centres.[1] Among them, enormous stereoselective catalytic versions involving classical Diels–Alder reactions and 1,3-dipolar cycloadditions have been well developed.[2] Nevertheless, the studies on higher-order asymmetric cycloadditions of substrates having more than 6π-electrons are still in infancy,[3] probably due to the regio- and chemoselectivity, the lack of periselectivity, and the extra challenge of transferring stereochemical information remotely.[4] When it comes to the isobenzofulvene, which has only transient existence generally requiring in situ formation during the reaction, there still are very limited relevant examples to date, though it has a long history to be known to display various cycloaddition modes serving as an 8π- or 10π-synthon.[5]

In 1968, Hafner and Bauer introduced an amino substituent into the exocyclic carbon to stabilize the isobenzofulvene species, and accomplished the [10+2] cycloaddition reaction with *N*-phenylmaleimide (Scheme 1a).[6] In 2017, inspired by this strategy, Jørgensen and co-workers disclosed the first catalytic formation of chiral 8-amino isobenzofulvene intermediates, which facilitated the highly stereoselective [8+2] cycloadditions with nitroalkenes to produce complex benzonorbornene architectures, probably through a cascade [10+4]/3,3-rearrangement process.[7a] They further developed an asymmetric [10+4] cycloaddition reaction by employing a type of newly designed electron-deficient dienes (Scheme 1b).[7b] However, to the best of our knowledge, the asymmetric [10+2] cycloaddition reaction involving the isobenzofulvene-type intermediates has not been achieved yet.



Scheme 1. The higher-order cycloadditions involving isobenzofulvene 10π-intermediates.

Recently, we reported the first asymmetric intermolecular [6+2] cycloaddition reaction of α′-alkylidene-2-cyclopentenones and 3-olefinic (7-aza)oxindoles by forming active 4-amino pentafulvene intermediates.[8] We also noticed a literature work, in which 2-benzylidene-1-indanone could undergo formal [10+2] cycloaddition-type dimerization under basic conditions, probably through generating a dearomative 1-hydroxyl isobenzofulvene anion intermediate (Scheme 1c).[9] Therefore, we envisioned that the asymmetric cross formal [10+2] cycloaddition reaction of 2-alkylidene-1-indanones with different activated alkenes might be feasible under suitable catalytic conditions, by forming active dearomative isobenzofulvene species, as outlined in Scheme 1c. As the initial attempts by using (*E*)-2-benzylidene 1-indanone **1a** and an amine catalyst to generate the possible active 1-amino isobenzofulvene intermediate resulted in no success,[10] we turned to employ the phase transfer catalysis (PTC),[11] which might more easily deprotonate the benzylic CH of substrate **1a** to form the corresponding 1-hydroxyl iaobenzofulvene anion. It was found that the cross formal [10+2] cycloadduct **3a** was indeed produced for the combination of enone **1a** and 3-olefinic oxindole **2a** in the presence of tetrabutylammonium bromide (TBAB, 20 mol%) and excess Cs_2CO_3, albeit in a low yield with fair diastereoselectivity (Table 1, entry 1). Unfortunately, almost no reaction occurred when a chiral PTC **C1** derived from cinchonidine was used (Table 1, entry 2). It has been disclosed that, with the assistant of dense cyano substituents, isobenzofulvenes could serve as strong acids.[12] Therefore,

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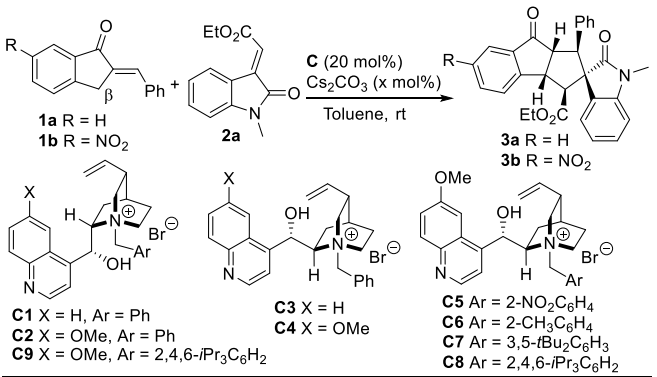
Table 1. Screening conditions for asymmetric cross formal [10+2] cycloaddition reaction[a]

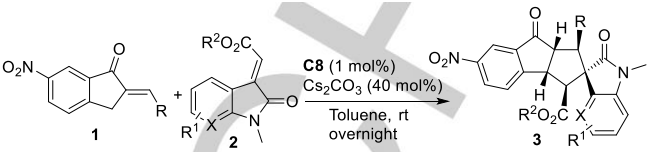


Entry	Cat	Cs_2CO_3 (x mol%)	*t* (h)	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1[e]	TBAB	120	24	**3a**, 30	4:1	/
2[e]	**C1**	120	24	**3a**, <5	/	/
3	**C1**	120	2	**3b**, 88	10.1:1	–30
4	**C2**	120	2	**3b**, 94	9:1	–64
5	**C3**	120	2	**3b**, 94	9:1	58
6	**C4**	120	2	**3b**, 94	>19:1	72
7	**C4**	60	2	**3b**, 90	>19:1	72
8	**C4**	40	2	**3b**, 85	>19:1	71
9	**C4**	20	2	**3b**, 90	>19:1	72
10	**C5**	20	2	**3b**, 95	19:1	82
11	**C6**	20	2	**3b**, 87	>19:1	81
12	**C7**	20	2	**3b**, 89	19:1	61
13	**C8**	20	2	**3b**, 72	>19:1	93
14[f,g]	**C8**	40	3	**3b**, 98	>19:1	96
15[f,h]	**C8**	40	3	**3b**, 94	>19:1	95
16[f,i]	**C8**	40	12	**3b**, 94	>19:1	95
17[f,j]	**C8**	40	24	**3b**, 59	13.3:1	90
18[i,k]	**C8**	40	12	**3b**, 92	>19:1	90
19[f,h]	**C9**	40	12	**3b**, 95	>19:1	–83

[a] Unless other noted, the reactions were conducted with enone **1b** (0.03 mmol), acceptor **2a** (0.025 mmol), Cs_2CO_3 (x mmol) and PTC (20 mol%) in toluene (0.5 mL) at rt. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] With enone **1a** and stirred at 50 °C. [f] On a 0.1 mmol scale (for **2a**). [g] With 2 mol% **C8**. [h] With 1 mol% **C8**. [i] With 0.5 mol% **C8**. [j] With 0.1 mol% **C8**. [k] On a 1.0 mmol scale (for **2a**).

introducing an electron-withdrawing group to 1-indanone motif would significantly increase its β-proton acidity.[13] To our delight, the reaction between **1b** bearing a 6-nitro group and **2a** proceeded smoothly catalyzed by **C1**, affording the desired product **3b** in 88% yield with high diastereoselectivity, albeit with low enantioselectivity, probably because the reactive site is far from the ion pair complex (Table 1, entry 3). The following screenings (Table 1, entries 4–6) indicated that catalyst **C4** from quinidine exhibited better stereocontrol (Table 1, entry 6), and the base loadings could be significantly reduced (Table, entries 7–9). Consequently, a few ammonium salts **C5**–**C8** were tested (Table 1, entries 10–13), and excellent enantioselectivity was obtained for the newly designed **C8** with a bulky 2,4,6-triisopropylbenzyl group, albeit in a moderate yield (Table 1, entry 13). Pleasingly, outstanding data could be attained even by dramatically decreasing the catalyst loadings to 2–0.5 mol% (Table 1, entries 14–16), whereas incomplete conversion with slightly reduced stereoselectivity was observed with 0.1 mol% **C8** (Table 1, entry 17). We also conducted the reaction at a 1.0 mmol scale using 0.5 mol% **C8**, and similarly good data were achieved (Table 1, entry 18). The corresponding enantiomer of **3b** could be obtained in a good *ee* value under the catalysis of **C9** derived from quinine (Table 1, entry 19).

Table 2. Substrate scope and limitations of asymmetric cross formal [10+2] cycloadditions[a]



Entry	R	R^1, R^2	Yield (%)[a]	*dr*[c]	*ee* (%)[d]
1[e]	Ph	H, Et	**3b**, 94 (95)	>19:1	95[f] (–83)
2[e]	2-$CH_3C_6H_4$	H, Et	**3c**, 92 (58)	>19:1	92 (–78)
3	3-$CH_3C_6H_4$	H, Et	**3d**, 89	>19:1	94
4	4-$CH_3C_6H_4$	H, Et	**3e**, 98	>19:1	95
5	3-$CH_3OC_6H_4$	H, Et	**3f**, 91	>19:1	93
6	2-BrC_6H_4	H, Et	**3g**, 94	>19:1	93
7[e]	4-BrC_6H_4	H, Et	**3h**, 96 (99)	>19:1	96 (–87)
8	4-$CF_3C_6H_4$	H, Et	**3i**, 95	>19:1	96
9	2-Furyl	H, Et	**3j**, 82	>19:1	91
10	Cyclopropyl	H, Et	**3k**, 96	>19:1	85
11	Cyclohexyl	H, Et	**3l**, 96	>19:1	90
12	Ph	H, *t*Bu	**3m**, 94	>19:1	94
13	Ph	7-Me, Et	**3n**, 95	>19:1	96
14	Ph	5-MeO, Et	**3o**, 96	>19:1	95
15[e]	Ph	6-MeO, Et	**3p**, 99 (53)	>19:1	95 (–85)
16[e]	Ph	5,7-Me_2, Et	**3q**, 93 (98)	>19:1	95 (–85)
17	Ph	5-CF_3O, Et	**3r**, 96	10.1:1	85
18	Ph	5-F, *t*Bu	**3s**, 97	19:1	89
19	Ph	5-Cl, *t*Bu	**3t**, 95	10.1:1	82
20	Ph	5-Br, *t*Bu	**3u**, 95	19:1	87
21[e]	Ph	6-Br, *t*Bu	**3v**, 95 (99)	19:1	89 (–83)
22	Ph	7-Br, *t*Bu	**3w**, 93	>19:1	89
23[g]	Ph	H, *t*Bu	**3x**, 96	>19:1	85

[a] Unless other noted, the reactions were conducted with **1** (0.12 mmol), **2** (0.1 mmol, X = CH), Cs_2CO_3 (0.04 mmol) and PTC **C8** (1 mol%) in toluene (2 mL) at rt overnight. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Data in parentheses were obtained with **C9** (1 mol%). [f] The absolute configuration of enantiopure **3b** was determined by X-ray analysis.[14] The other products were assigned by analogy. [g] X = N.

With the optimal catalytic conditions in hand, the scope and limitations of both types of substrates were investigated. The reactions were generally conducted with only 1 mol% **C8** and 40 mol% Cs_2CO_3 at rt overnight. The results are summarized in Table 2. The enones **1** condensed from 6-nitro-indanone and diverse arylaldehydes or 2-furfural were well tolerated in the reactions with acceptor **2a**, and consistently high yields with excellent diastereo- and enantioselectivity were obtained (Table 2, entries 2–9). Notably, the substrate **1** bearing a cyclopropyl or cyclohexyl group was also compatible (Table 2, entries 10 and 11). On the other hand, the substitution patterns of the acceptors **2** were explored. The substrate **2** having a *t*-butyl ester group gave similarly excellent results (Table 2, entry 12). Moreover, excellent yields and stereoselectivity were also obtained by

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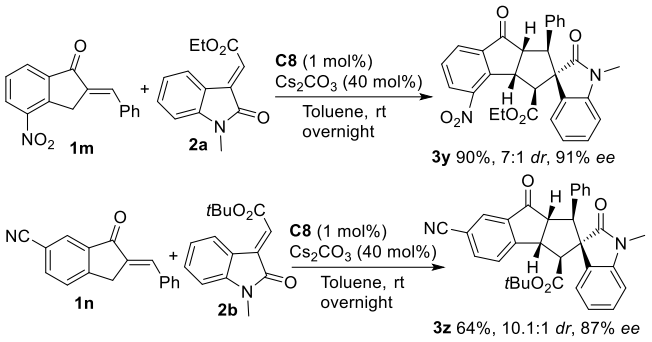
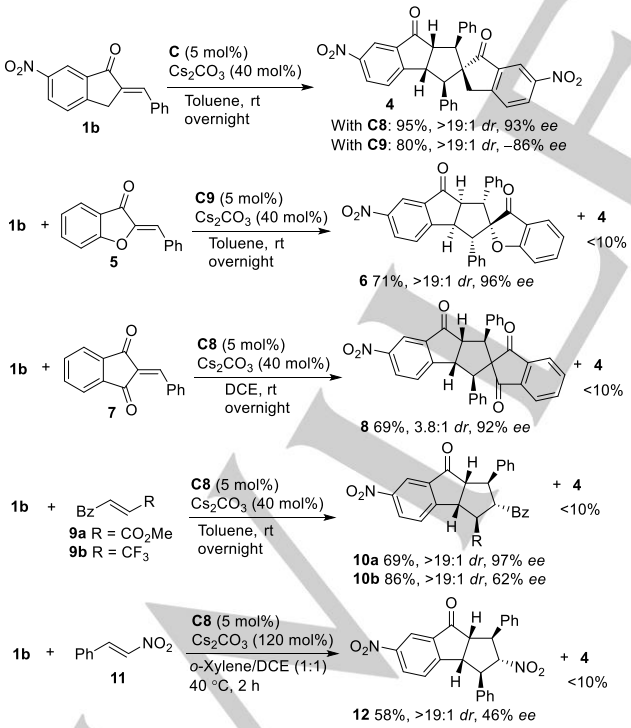
introducing diverse electron-donating groups into the oxindole motif (Table 2, entries 13–16), whereas slightly reduced diastereo- and enantioselectivity were generally observed for those with an electron-withdrawing group (Table 2, entries 17–22). In addition, good data were gained for an alkene having a 7-azaindole motif (Table 2, entry 23). A few substrate combinations were also tested with PTC **C9**, and the corresponding enantiomers (of compounds **3**) were produced with moderate to high enantioselectivity (Table 2, data in parentheses).



Scheme 2. Exploration of more 2-benzylidene-1-indanone substrates.

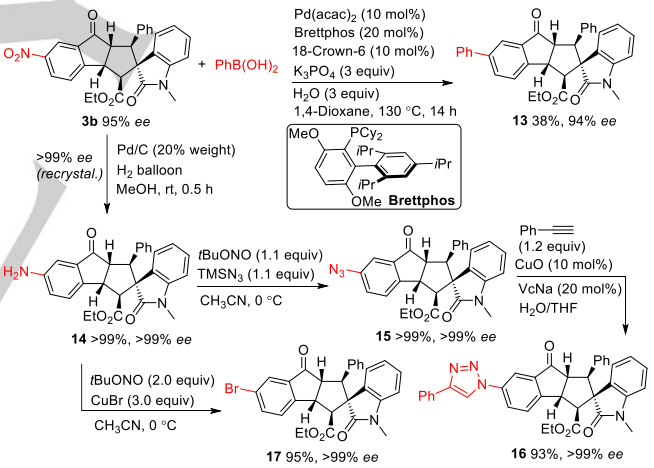
As illustrated in Scheme 2, 4-nitro-2-benzylidene-1-indanone **1m** also showed high reactivity with acceptor **2a** under the same catalytic conditions, and the product **3y** was obtained in excellent yield and enantioselectivity, albeit with modest diastereoselectivity.[15] Nevertheless, the reactivity was obviously decreased for the substrate **1n** with a 6-cyano group, whereas good diastereo- and enantioselectivity were obtained for the desired product **3z**.



Scheme 3. Exploration of more activated alkenes.

Although highly chemoselective cross [10+2] cycloaddition reaction was observed for the combination of enone **1b** and 3-olefinic oxindole **2a**, the asymmetric dimerization of **1b** indeed took place in the absence of a suitable 2π partner. As illustrated in Scheme 3, chiral dimer **4** was obtained in excellent results under the catalysis of PTC **C8** (5 mol%), and its enantiomer could be similarly produced with PTC **C9**. Importantly, the chemoselective cross [10+2] cycloaddition reaction was also applicable for the combination of enone **1b** with activated alkenes **5** and **7**, producing the corresponding fused frameworks **6** and **8**, respectively, in moderate yields with outstanding enantioselectivity, whereas only trace amounts of dimerization product **4** were observed. Moreover, other activated alkenes **9** and **11** with α,β-disubstitution patterns were explored, and the chemoselective cross [10+2] cycloadducts **10** and **12** were successfully yielded, though modest enantiocontrol was observed in some cases. Thus, the structural diversity and versatility of the related hydrocyclopenta[a]indene skeleton could be significantly broadened.[16]

The nitro group of substrate **1b** is not only crucial for activating the [10+2] reaction, but also enables a variety of transformations to introduce more functional diversity. As outlined in Scheme 4, a denitrative Suzuki-type coupling reaction with product **3b** was directly conducted with phenylboronic acid at 130 °C,[17] giving product **13** in a fair yield due to incomplete conversion. Moreover, the nitro group was easily reduced to afford amine **14**, and an azido group was efficiently introduced using an established procedure.[18] The resulting **15** could be further converted to product **16** after a click reaction. In addition, a bromide product **17** was also facilely available from amine **14** via a modified Sandmeyer-type reaction.[19]



Scheme 4. Transformations of chiral [10+2] cycloadduct **3b**. VcNa: sodium ascorbate.

In conclusion, we have disclosed that activated 2-alkylidene-1-indanones could be effectively converted to dearomative 1-hydroxyl isobenzofulvene-type species under chiral phase transfer catalytic conditions, and undergo highly chemoselective cross formal [10+2] cycloaddition reactions with a diversity of electron-deficient alkene substrates. Excellent diastereo- and enantioselectivity were generally obtained by employing a newly designed cinchona-based ammonium salt with a bulky substituent at quite low loadings (1 mol%), giving a spectrum of fused frameworks with highly structural complexity and versatility, though the reactive site is far away from the chiral ion pair complex. To the best of our knowledge, it also represents the first example of asymmetric [10+2] cycloaddition reaction involving isobenzofulvene-based 10π-intermediates. More work to expand this synthetic strategy is under way and the results will be reported in due course.

Experimental Section

Procedure for the synthesis of [10+2] cycloadduct 3b.

(*E*)-2-Benzylidene-6-nitro-1-indanone **1b** (31.8 mg, 0.12 mmol), 3-olefinic oxindole **2a** (23.1 mg, 0.10 mmol), PTC **C8** (0.6 mg, 0.001 mmol), and Cs_2CO_3 (13.0 mg, 0.04 mmol) were added to a test tube followed by the addition of toluene (2.0 mL). The mixture was stirred at room temperature overnight, and monitored by TLC. After completion, the product **3b** was obtained by flash chromatography on silica gel (EtOAc/petroleum ether = 1/10–1/8): White solid, 48.6 mg, 94% yield; mp: 137–140 °C; >19:1 *dr*; 95% *ee*, determined by HPLC analysis [Daicel Chiral IA (*n*-hexane/*i*PrOH = 60/40), 1.0 mL/min, λ = 254 nm, t (major) = 16.30 min, t (minor) = 21.25 min]; $[\alpha]_D^{25}$ = +49.5 (*c* = 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.58 (d, *J* = 2.1 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.21 (td, *J* = 7.8, 0.9 Hz, 1H), 7.10–7.01 (m, 4H), 6.95 (dd, *J* = 7.8, 1.3 Hz, 2H), 6.59 (d, *J* = 7.8 Hz, 1H), 4.97 (t, *J* = 8.9 Hz, 1H), 4.12 (dd, *J* = 11.7, 8.8 Hz, 1H), 3.93 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.78 (d, *J* = 11.8 Hz, 1H), 3.72 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.67 (d, *J* = 9.0 Hz, 1H), 3.02 (s, 3H), 0.68 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.0, 175.7, 170.3, 161.0, 148.8, 143.7, 136.7, 133.7, 130.0, 129.1, 127.9, 127.9, 127.8, 127.7, 126.5, 124.0, 122.4, 112.0, 108.2, 66.5, 61.2, 56.5, 56.1, 54.5, 45.5, 26.3, 13.4; HRMS (ESI): Calcd. for $C_{29}H_{25}N_2O_6^+$ ($[M+H]^+$): 497.1707, found: 497.1707.

Acknowledgements

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Keywords: higher-order cycloaddition • isobenzofulvene • [10+2] cycloaddition • phase-transfer catalysis • chemoselectivity

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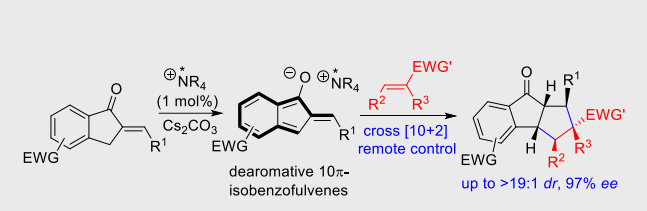

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Page No. – Page No.
Asymmetric Formal Cross [10+2] Cycloaddtions of 2-Alkylidene-1-indanones and Activated Alkenes under Phase-Transfer Catalysis

Higher order cycloaddition: The activated 2-alkylidene-1-indanones can form dearomative 1-hydroxyl isobenzofulvene anions under mild phase transfer conditions, and undergo highly chemoselective cross formal [10+2] cycloaddtion reactions with a diversity of electron-deficient alkenes. An array of polyhydrocyclopenta[*a*]indene frameworks with multiple functionalities were generally furnished in excellent diastereo- and enantioselectivity by employing a newly developed cinchona-based ammonium salt, even at 1 mol% loadings.