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Phase-Transfer and Other Types of Catalysis with Cyclopropenium Ions

Jeffrey S. Bandar^[a], Anont Tanaset^[a], and Tristan H. Lambert Prof.^{*,[a]}

^[a] Department of Chemistry, Columbia University, 3000 Broadway New York, NY 10027 (USA)

Abstract

This work establishes the cyclopropenium ion as a viable platform for efficient phase transfer catalysis of a diverse range of organic transformations. The amenability of these catalysts to large-scale synthesis and structural modification is demonstrated. Evaluation of the molecular structure of an optimal catalyst reveals some unique structural features of these systems. Finally a discussion of electronic charge distribution underscores an important consideration for catalyst design.

Keywords

phase transfer catalysis; cyclopropenium; aromatic ion

Phase transfer catalysis (PTC) has proven to be a highly advantageous strategy for reaction promotion.¹ Phase transfer catalysts facilitate reactions of substances that are heterogeneously distributed in immiscible phases, with catalysis generally operating via the transfer of an anionic species from the aqueous (or solid) phase to the organic phase. PTC methods offer a number of important advantages, namely: (1) decreased dependence on organic solvents; (2) excellent scalability and inherent compatibility with moisture; (3) enhancement of reactivity, which permits shortened reaction times and increased yields; (4) ability to substitute costly and inconvenient reagents (such as LDA) for simple aqueous bases (such as KOH); and (5) amenability to enantioselective variants.^{2, 3} For these reasons, phase transfer catalysis has emerged as a widely used technology throughout the domains of pharmaceutical, agrochemical, and materials chemistry.

Traditionally, phase transfer catalysts have been largely restricted to the group 15 onium compounds, namely ammonium and phosphonium salts (Figure 1a).⁴ Chiral ammonium salts, in particular, have proven to be quite effective at promoting asymmetric PTC. On the other hand, the synthesis of complex phase-transfer catalysts is oftentimes lengthy and/or challenging, which presents a barrier to rapid catalyst screening and reaction optimization. Given the substantial industrial reliance on practical PTC-based manufacturing technologies,⁵ we envisioned that introduction of a versatile new phase transfer catalyst platform would be of high interest to the synthetic community. In this Communication, we

tl2240@columbia.edu.

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demonstrate that tris(dialkylamino)-cyclopropenium (TDAC) salts⁶ are a viable new PTC platform that offers excellent reactivity in a range of PTC-based transformations.⁷

Amine-substituted cyclopropenium ions have been known for more than 40 years,⁸ but have recently attracted particular attention for their unique structural and reactivity properties in the context of free carbenes,⁹ metal or main-group ligands,¹⁰ ionic liquids,¹¹ and polyelectrolytes.¹² Given their amenability to scalable preparation and their inherent modularity, we envisioned that TDAC ions could serve as an attractive new class of phase-transfer catalysts. At the outset, however, it was an open question as to whether these strained carbocations would be compatible with the basic and nucleophilic environments characteristic of phase-transfer reactions, given the known propensity of these materials to undergo hydrolysis or ring-opening reactions (Figure 1b).⁶

The synthesis of TDAC ions most conveniently utilizes pentachlorocyclopropane, which is accessible in large quantities (Figure 1c).¹³ As a demonstration of the ease of synthesis of these materials, TDAC **1**•Cl was prepared on a 75 g scale in a single flask in 95% yield. TDAC ions of this type are stable, free-flowing powders that are easily modified through variation of the amine component or through ion exchange.

With ample quantities of **1**•Cl and other TDAC salts in hand, we first investigated the ability of these materials to function as effective phase transfer catalysts for enolate alkylation. With the goal of establishing preliminary structure-activity parameters, we screened a range of TDAC candidates as catalysts in the transformation depicted in Table 1. Several trends emerged from our preliminary catalyst screen. First, comparison of tris-symmetrical cyclopropenium salts (entries 1a-d) revealed a positive correlation between catalyst lipophilicity and reaction efficiency. The dihexylamino-substituted catalyst (entry 1c) was more reactive than the dimethylamino or dibutylamino analogs (entries 1a,b), while the highly polar morpholine-substituted cyclopropenium was largely ineffective in this reaction (entry 1d). The bis(dicyclohexyl)cyclopropenium scaffold bearing a diethylamino head group (**1**) was found to be highly reactive, particularly when iodide – rather than chloride – was used as the counterion (entries 2a vs. 2b). We believe that the iodide counterion serves the dual function of activating the electrophile (BnBr → BnI) and facilitating PTC. Interestingly, the protonated analog, **2**, though completely inactive in toluene (entry 3a), promoted the reaction in CH₂Cl₂ with excellent efficiency (entry 3b). Having identified **1**•I and **2**•Cl as optimal catalysts for this transformation, we next demonstrated their compatibility with a range of “green” solvents, including ethyl acetate, isopropyl acetate, cyclopentyl methyl ether (47–68% isolated yield, entries 2c–e), and 2-butanone (76% isolated yield, 2h, entry 3c). Notably, the cyclopropenium catalysts possess levels of efficiency comparable or superior to those exhibited by several established phase transfer catalysts (entries 4–6).

We next sought to probe the scope of this alkylation chemistry with respect to the electrophilic and nucleophilic coupling partners. For each substrate pair, both System A (**1**•I, toluene, 50% KOH) and System B (**2**•Cl, CH₂Cl₂, 50% KOH) were evaluated for reaction time and yield. The results presented in Table 2 reflect the optimal conditions for each transformation. Thus, as shown in Table 2 (top), cyclopropenium **1**•I effectively catalyzes

benzylation of a range of pro-nucleophiles, including ketones (entries 1 and 3), esters (entry 2), and amides (entry 4). In the latter substrate, we observed rapid double alkylation of the oxindole system at both the enolate and nitrogen positions. We next examined addition of a glycine imine to a range of electrophiles (Table 2, bottom). As shown, the glycine imine readily participates in alkylation or Michael addition with excellent efficiency (entries 5–8).

We have also investigated an alternative mode of catalysis for these cyclopropenium salts with the addition of acid chlorides to epoxides en route to synthetically useful halohydrin ester adducts.¹⁴ Thus, under catalysis by 2.5 mol% **1**•Cl, phenylacetyl chloride was observed to rapidly add to a range of terminal epoxides with good yields and regioselectivities (Table 3, entries 1–4). Addition of phenylacetyl chloride to styrene oxide also proceeded in excellent yield, albeit with diminished regioselectivity (entry 5). More hindered epoxides were generally less amenable to acid chloride addition (entry 6); however reaction of cyclohexene oxide with phenylacetyl chloride proceeded in 64% yield after 2h (entry 7). In comparisons with other PTCs, **1**•Cl (entry 1) was notably faster and more regioselective than either tetrabutylammonium chloride (entry 8) or an imidazolium salt (entry 9), and equal to tetraphenylphosphonium chloride (entry 10). We believe this reaction occurs via nucleophilic opening of the epoxide by chloride ion, followed by acylation of the resulting cyclopropenium alkoxide.

This epoxide-opening chemistry was subsequently expanded to encompass carbon dioxide fixation.¹⁵ As shown in Table 4, a series of terminal epoxides were exposed to 2.5 mol% **1**•Cl under neat conditions with a CO₂ balloon (1 atm). The adducts were isolated in good yields within 20–48h (entries 1–3). The hindered cyclohexene oxide was somewhat less amenable to this transformation, delivering product in only 28% yield after 5–7 days (entry 4).

With the goal of establishing cyclopropenium ions as a general class of phase transfer catalyst, we have also demonstrated the ability of this system to promote a wide array of mainstay PTC-based transformations. As shown in eqs. 1–4, the cyclopropenium catalysts were found to be effective in a range of diverse settings, including: phenol alkylation, azide substitution, alcohol oxidation, and cyclopropanation. Importantly, in each of these cases no reaction was observed in the absence of catalyst.

(1)

(3)

(4)

Single-crystal X-ray analysis of **1**•Cl revealed some interesting structural features that may prove important for the design of chiral catalysts based on this architecture (Figure 2a). Most notably, steric crowding induces the dialkylamino substituents to adopt a significant dihedral angle relative to the cyclopropenium ring¹⁶ by 17° in the case of the dicyclohexylamino groups and 37° for the diethylamino group. The substantial torquing of the diethylamino moiety can clearly be seen in the edge view (Figure 2b). How the crystal-packing conformation of **1** correlates to its solution-phase dynamics is not known, but this torquing phenomenon is undoubtedly an unavoidable aspect of these ring systems that should be taken into account when considering chiral variants of these catalysts.

Finally, although the Lewis structure depiction of TDAC ions indicates a formally carbocationic ring, the cyclopropenium core is in fact a site of relative electron richness.¹⁷ This feature is clearly seen in an electron-density map of tris(dimethylamino)cyclopropenium ion, which shows that the areas of maximal electron deficiency reside at the hydrogens of the peripheral methyl groups, as would be expected from a simple consideration of relative electronegativities and the TDAC HOMO^{17e} (Figure 2c). The implication of this charge distribution is that anions can be expected to associate with the edge, rather than the face, of the planar cyclopropenium. This expectation is supported by the unit cell view of the X-ray structure of **1**•Cl (Figure 2d), which clearly shows the chloride ions encapsulated by the dialkylamino substituents. Assuming these orientations translate to the solution phase, they are sure to be an important consideration for the design of functional cyclopropenium phase-transfer catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cyclopropenium Ions: a new class of phase transfer catalyst.

Figure 2.

Molecular structure of **1**. (a) Face view. (b) Edge view. The curved arrows and associated degree labels indicate the dihedral angle of the cyclopropenium ring and the C-N-C plane of the amino substituents. The chloride counterion has been removed for clarity. (c) Electron density map of trisaminocyclopropenium ion, calculated at the B3LYP/6-31G** level. (d) Unit cell of **1**·Cl.

Table 1

PTC of enolate alkylation: catalyst optimization studies.

entry	Catalyst		Solvent	Conv. (%) ^[a]
1		(a) NR ₂ =NMe ₂ (b) NBU ₂ (c) NHex ₂ (d) NMorph	toluene toluene toluene toluene	66 62 97 13
2		(a) X = Cl (b) I (c) I (d) I (e) I	toluene toluene EtOAc iPrOAc <i>c</i> -C ₅ H ₉ -OCH ₃	79 96 53 47 68
3		(a) (b) (c) ^[b]	toluene CH ₂ Cl ₂ CH ₃ C(O)C ₂ H ₅	0 94 76
4	NBU ₄ Cl		toluene	80
5	PPh ₄ Cl		toluene	0
6			toluene	98

^[a] Percent conversion after 24h, as measured by ¹H NMR, average of two runs. Entries 2c-e and 3c represent isolated yields from an average of two runs.

^[b] 2 h reaction time.

Table 2

PTC of enolate alkylation: substrate scope.^[a]

System A:	10 mol% 1 · I [−] PhMe, 50% KOH	System B:	10 mol% 2 CH ₂ Cl ₂ , 50% KOH
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entry	product	System	Time (h)	Yield (%) ^[a]
1		A	0.5	44
2		A	40	99
3		A	0.15	80
4		A	0.15	98
5		B	20	97
6		B	12	99
7		B	1	95
8		A	1	86

^[a] isolated yield, average of two runs.

Table 3

Cyclopropenium chloride-catalyzed addition of acid chlorides to epoxides.

entry	epoxide	catalyst	time (h)	yield (%) ^[a]	A:B
1		1 · Cl	4	68	6.3:1
2		1 · Cl	3	91 ^[b]	>20:1
3		1 · Cl	2	74 ^[b]	>20:1
4		1 · Cl	5	65	>20:1
5		1 · Cl	3	95 ^[b]	1.9:1
6		1 · Cl	24	<15	--
7		1 · Cl	2	64	--
8 ^[c]		NBu ₄ Cl	30	67	2.4:1

entry	epoxide	catalyst	time (h)	yield (%) ^[a]	A:B
9 ^[c]			30	48	2.3:1
10 ^[c]		PPh ₄ Cl	4	69	6.1:1

^[a] isolated yields.

^[b] 1.0 equiv of pyridine and 3.0 equiv of acid chloride used; no background reaction was observed.

^[c] yields determined by ¹H NMR.

Table 4

Cyclopropenium chloride-catalyzed addition of carbon dioxide to epoxides.

entry	epoxide	product	time (h)	yield (%) ^[a]
1			48	72
2			20	90
3			36	89

entry	epoxide	product	time (h)	yield (%) ^[a]
4			5-7 d	28

^[a] isolated yields.