**Carbenes**

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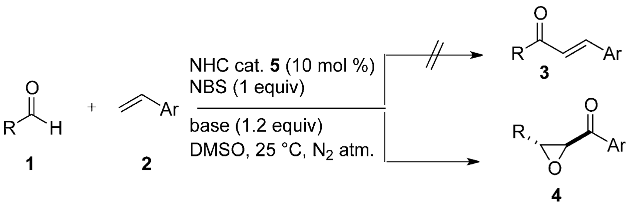
# N-Heterocyclic Carbene Catalyzed Oxidative Coupling of Alkenes/α-Bromoacetophenones with Aldehydes: A Facile Entry to α,β-Epoxy Ketones

*Rambabu N. Reddi, Pragati K. Prasad, and Arumugam Sudalai**

**Abstract:** *A novel, N-heterocyclic carbene (NHC) catalyzed direct oxidative coupling of styrenes with aldehydes has been described for the synthesis of α,β-epoxy ketones in good yields. This unprecedented regioselective oxidative coupling employs NBS/DBU/DMSO (DBU = 1,8-diazabicyclo [5.4. 0] undec-7-ene, DMSO = dimethylsulfoxide, NBS = N-bromosuccinimide) as an oxidative system at ambient conditions. Additionally, first NHC-catalyzed Darzens reaction of α-bromoketones and aldehydes under mild reaction conditions has also been described. Interestingly, mechanistic studies have revealed the preferred reactivity of NHC with alkene/α-bromoketone rather than aldehydes, thus proceeding via the ketodeoxy Breslow intermediate.*

Epoxy ketones are among the most versatile building blocks in organic synthesis because of their dense functionalization. Further, they can be reliably functionalized to provide numerous products (e.g. pharmaceuticals, natural products, agricultural chemicals, fragrances, and inhibitors of cytosolic epoxide hydrolases) including α- and β-carbonyls, α,β-epoxy alcohols, 1,3-diols, etc.[1] In general, α,β-epoxy ketones can be prepared either by the Darzens reaction of α-halocarbonyl compounds with aldehydes under strong basic conditions[2] or epoxidation of α,β-unsaturated ketones, with various oxidants, catalyzed by Lewis acids or phase-transfer catalysts.[3] An alternative method of oxidative coupling of aldehydes with styrenes catalyzed by base, with TBHP as an oxidant, has also been reported for its synthesis.[4] However, these methods require either prefunctionalized starting materials, costly metal catalysts, or often employ a large excess of aldehydes and oxidants (TBHP, $H_2O_2$) at high temperatures, thus resulting in low atom economy of the process.

Organocatalyzed reactions represent an attractive alternative to metal-catalyzed processes because of their low cost and benign environmental impact in comparison to organometallic catalysis. As organocatalysts, N-heterocyclic carbenes (NHCs) catalyze a wide range of C−C, C−O, and C−N bond-forming reactions involving umpolung of the functional group, with the carbonyl carbon atom acting as a transient nucleophile.[5] NHC catalysts, because of their moderate nucleophilicity, are limited to reactions with carbonyl compounds and electron-deficient alkenes only,[6] and their reactions with other electrophiles remain elusive.[7] In continuation of our earlier studies on NHC-catalyzed reactions,[7] we envisioned that the Breslow intermediate from the aldehyde **1** and NHC **5** could regioselectively open the bromonium ion **A** (for structure see Scheme 5), formed in situ from the alkene **2** and NHC, to afford, after HBr elimination, the corresponding α,β-unsaturated ketone **3** (Scheme 1). Surprisingly, the reaction took a different course, thus affording the epoxy ketones **4** in high yields. To the best of our knowledge, the direct coupling of aldehydes with alkenes under NHC catalysis has not been reported. Herein, we describe NHC-catalyzed oxidative coupling of styrenes and aldehydes to afford the corresponding α,β-epoxy ketones in good yields and in a highly regio- and diastereoselective manner, by using NBS/DBU/DMSO as an oxidative system under an $N_2$ atmosphere.



*Scheme 1.* NHC-catalyzed oxidative coupling of alkenes with aldehydes. DBU = 1,8-diazabicyclo [5.4. 0] undec-7-ene, DMSO = dimethylsulfoxide, NBS = *N*-bromosuccinimide.

To begin with, when styrene (**2a**; 1 mmol) was treated with a mixture containing *p*-nitrobenzaldehyde (**1e**; 1.1 mmol), NBS (1 mmol), and $Et_3N$ (1.2 mmol) in the presence of the NHC catalyst **5a** (10 mol%; for structure see Figure 1) at 25 °C in DMSO under a completely inert atmosphere, the α,β-epoxy ketone **4e** was obtained in 56% yield upon isolation, with an excellent diastereomeric ratio (*trans/cis* = 98:2; Table 1). It is unusual that the ketone group in **4e** is formed from the styrenic counterpart by benzylic oxidation while the epoxide moiety is obtained from the aldehydic coupling partner. To improve the yield of **4e**, other NHC catalysts were examined (Figure 1). Among the catalysts screened, the thiazolium-based catalysts **5d** and **5e** were found to be quite efficient for the oxidative coupling reaction (up to 66% yields), while the imidazolium-based precatalysts gave only moderate yields (up to 45%; Table 1; entries 1–5). Surprisingly, the triazolium-based NHC catalysts **5f** and **5g** gave extremely low yields (18 and 13%, respectively) of the

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[*] R. N. Reddi,[+] P. K. Prasad,[+] Dr. A. Sudalai
Chemical Engineering and Process Development Division
National Chemical Laboratory
Pashan Road, Pune, 411008 (India)
E-mail: a.sudalai@ncl.res.in

[+] These authors contributed equally to this work.

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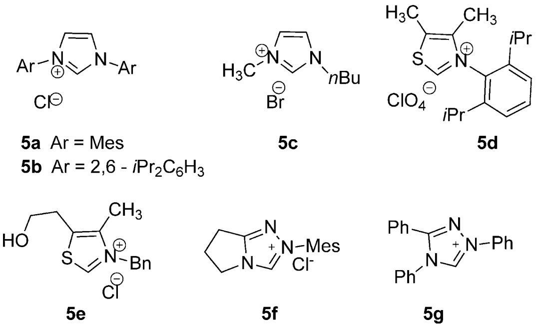
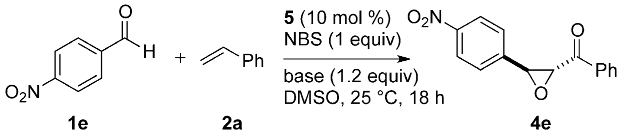


*Figure 1.* Some of the NHC precatalysts used. Mes = 2,4,6-trimethylphenyl.

*Table 1:* NHC-catalyzed oxidative coupling of 4-nitrobenzaldehyde (**1e**) and styrene (**2a**): Optimization studies.[a]



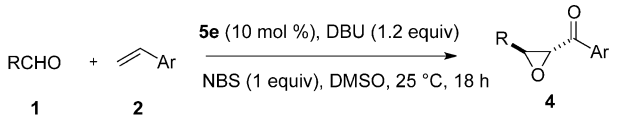
| Entry | **5** (10 mol%) | Base | Yield [%][b] |
|---|---|---|---|
| 1 | **5a** | $Et_3N$ | 56 |
| 2 | **5b** | $Et_3N$ | 45 |
| 3 | **5c** | $Et_3N$ | 37 |
| 4 | **5d** | $Et_3N$ | 58 |
| 5 | **5e** | $Et_3N$ | 66 |
| 6 | **5f** | $Et_3N$ | 18 |
| 7 | **5g** | $Et_3N$ | 13 |
| 8 | **5e** | NaH | 54 |
| 9 | **5e** | $Cs_2CO_3$ | 24 |
| 10 | **5e** | KO*t*Bu | 61 |
| 11 | **5e** | DBU | 72 (51)[c] (15)[d] |
| 12 | **5e** (5 mol%) | DBU | 41 (70)[e] |

[a] Reaction conditions: styrene (1 mmol), *p*-nitrobenzaldehyde (1.1 mmol), NHC precatalyst (**5a–e**; 10 mol%), base (1.2 mmol), and NBS (1 mmol) in DMSO at 25 °C for 18 h. [b] Yield of isolated product after column chromatographic purification. [c] NIS was used instead of NBS. [d] NCS was used as halogen source. [e] 20 mol% of catalyst **5e** was used.

desired product **4e**. Other solvents such as THF, $CH_3CN$, $CH_2Cl_2$, 1,4-dioxane, and DMF were unsuitable for the reaction. Also, DBU was found to be an excellent base for the reaction (72 % yield) while inorganic bases were only moderately active (up to 61 % yield; entries 8–11). Other *N*-halosuccinimides (halogen = I, Cl) were also screened to give **4e** in 51 and 15 % yields, respectively (entry 11). In addition, either lowering of the catalyst concentration or increase of the reaction temperature did not significantly improve the yield (entry 12).

With this optimized yield in hand, the NHC catalytic system consisting of **5e** (10 mol %), NBS (1 equiv), and DBU (1.2 equiv) in DMSO under an inert atmosphere was chosen for the study of the substrate scope. Accordingly, a variety of aromatic aldehydes (**1a–f**), having different groups such as bromo, chloro, methyl, and $NO_2$, etc. at various positions on the aromatic nucleus, were subjected to oxidative coupling (Table 2) with styrenes. For all the substrates studied, moderate to good yields (58–72 %) of the epoxy ketones **4a–f** were obtained (entries 1–6). Notably, aliphatic aldehydes such as heptanal (**1g**) and isovaleraldehyde (**1h**) afforded the corresponding epoxy ketones **4g** (51 %) and **4h** (62 %; entries 7 and 8). Remarkably, ethyl glyoxalate (**1i**) gave ethyl 3-benzoyloxirane-2-carboxylate (**4i**) in moderate yield (65 %; entry 9). Additionally, styrene-type substrates, having Br and Me groups on the benzene nucleus, were subjected to coupling with **1e** under the optimized reaction conditions and gave good yields of the corresponding α,β-epoxy ketones **4j** (64 %) and **4k** (69 %; entries 10 and 11). In the case of 1-octene (**2d**), the desired epoxy ketone **4l** was formed in 16 % yield. However, internal alkenes and terminal disubstituted alkenes failed to undergo this oxidative coupling reaction.

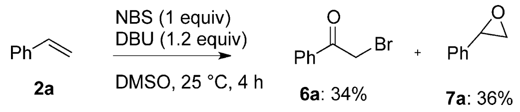
*Table 2:* NHC-catalyzed oxidative coupling of styrenes with aldehydes: Substrate scope.[a]



| Entry | Aldehyde (**1**) | Styrene (**2**) | Yield [%][b,c] | |
|---|---|---|---|---|
| 1 | benzaldehyde (**1a**) | styrene (**2a**) | **4a** | 61 |
| 2 | 4-$BrC_6H_4CHO$ (**1b**) | styrene | **4b** | 58 |
| 3 | 4-$ClC_6H_4CHO$ (**1c**) | styrene | **4c** | 63 |
| 4 | 4-$CNC_6H_4CHO$ (**1d**) | styrene | **4d** | 66 |
| 5 | 4-$NO_2C_6H_4CHO$ (**1e**) | styrene | **4e** | 72 |
| 6 | 2-$NO_2C_6H_4CHO$ (**1f**) | styrene | **4f** | 68 |
| 7 | 1-heptanal (**1g**) | styrene | **4g** | 51 |
| 8 | isovaleraldehyde (**1h**) | styrene | **4h** | 62 |
| 9 | ethyl glyoxalate (**1i**) | styrene | **4i** | 65 |
| 10 | 4-$NO_2C_6H_4CHO$ (**1e**) | 4-methylstyrene (**2b**) | **4j** | 64 |
| 11 | 4-$NO_2C_6H_4CHO$ (**1e**) | 4-bromostyrene (**2c**) | **4k** | 69 |
| 12 | benzaldehyde (**1a**) | 1-octene (**2d**)[d] | **4l** | 16 |

[a] For the reaction conditions, see the footnote [a] of Table 1. [b] Yield of product isolated after column chromatographic purification. [c] Diastereomeric ratios were found to be about 95:5 in each case as determined by HPLC and $^1H$ NMR analysess of the crude reaction mixture.
[d] 3 equiv of **2d** were used and the reaction time was 34 h.

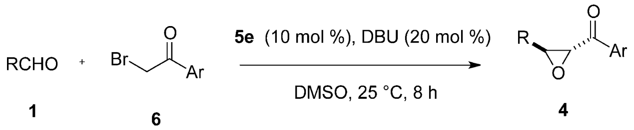
To probe the reaction mechanism, the following control experiments were conducted: a) no epoxy ketone product was formed in the absence of either the NHC catalyst or NBS; thereby establishing the fact that both of them are critical in this coupling reaction; b) when the NHC precatalyst **5e** was treated with NBS and DBU in DMSO in the absence of styrene and aldehyde, the NHC dimer **8** was isolated[11] in 40 % yield, and it was also formed in the absence of NBS. This result explains the fact that no reaction occurs between NBS and NHC; c) in the absence of aldehyde and NHC catalyst, with **2a** as a substrate, the phenacyl bromide **6a** and styrene epoxide **7a** were formed in 34 % and 36 % yields, respectively (Scheme 2); d) additionally, treatment of **6a** with **1e**, in the presence of **5e** and DBU under a $N_2$ atmosphere, afforded the desired product **4e** in 78 % yield, whereas **7a**, under similar reaction conditions did not undergo any reaction. Thus, it is proven that the coupling reaction proceeds through the respective α-bromoketones **6**, which subsequently react with aldehydes: indeed a conventional Darzens reaction.



*Scheme 2.* Control experiments to probe the mechanism.

Consequently, it was of interest to explore the first NHC-catalyzed Darzens reaction to see if it could overcome the disadvantages associated with the conventional reagent system (e.g. strong basic conditions, use of sulfur compounds and phase-transfer reagents). The results are presented in Table 3. Accordingly, various aromatic aldehydes having groups such as Cl, Br, CN, and NO$_2$ on the aromatic nucleus were subjected to the NHC-catalyzed Darzens reactions with the phenacyl bromides **6** and afforded the corresponding $\alpha,\beta$-epoxy ketones (**4a**–**e**) in high yields (entries 1–5). Also, 1-1-heptanal (**1g**) gave the corresponding epoxy ketone **4g** in 68% yield. Further, the substituted $\alpha$-bromoacetophenones **6b** and **6c** gave **4j** (71%) and **4k** (69%), respectively (entries 7 and 8). Interestingly, the aliphatic bromoketone **6d** gave the corresponding epoxy ketone **4l** in 54% yield. Remarkably, for its asymmetric version, the chiral NHC catalyst **5h** was used, and gave the corresponding chiral epoxy ketone **4e** in 62% yield with 56% enantiomeric excess (Scheme 3). The absolute configuration (2*S*, 3*R*) of (+)-**4e** was assigned based on comparison of its specific rotation with the reported value.[3h]

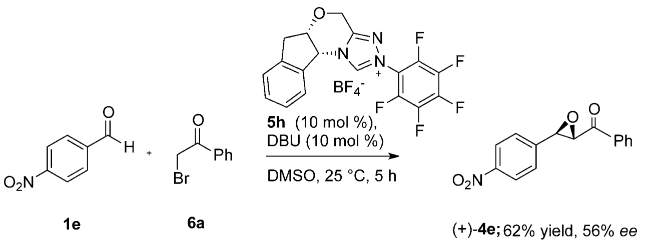
*Table 3:* NHC-catalyzed oxidative coupling of $\alpha$-bromoacetophenones with aldehydes: Substrate scope.[a]



| Entry | Aldehyde (**1**) | Ar (**6**) | Yield [%][b,c] |
|---|---|---|---|
| 1 | benzaldehyde (**1a**) | Ph (**6a**) | **4a** 71 |
| 2 | 4-BrC$_6$H$_4$CHO (**1b**) | Ph | **4b** 74 |
| 3 | 4-ClC$_6$H$_4$CHO (**1c**) | Ph | **4c** 75 |
| 4 | 4-CNC$_6$H$_4$CHO (**1d**) | Ph | **4d** 72 |
| 5 | 4-NO$_2$C$_6$H$_4$CHO (**1e**) | Ph | **4e** 78 (15)[d] (66)[e,f] |
| 6 | 1-heptanal (**1g**) | Ph | **4g** 68 |
| 7 | 4-NO$_2$C$_6$H$_4$CHO (**1e**) | 4-MeC$_6$H$_4$ (**6b**) | **4j** 71 |
| 8 | 4-NO$_2$C$_6$H$_4$CHO (**1e**) | 4-BrC$_6$H$_4$ (**6c**) | **4k** 69 |
| 9 | benzaldehyde (**1a**) | C$_6$H$_{11}$ (**6d**) | **4l** 54[g] |

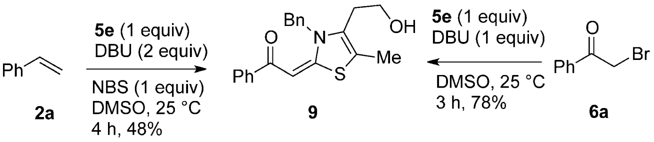
[a] Reaction conditions: $\alpha$-bromoacetophenones (1 mmol), aldehyde (1.1 mmol), NHC precatalyst **5e** (10 mol%), and DBU (20 mol%) in DMSO at 25 °C, for 12 h under N$_2$ atm. [b] Yield of product isolated after column chromatographic purification. [c] Diastereomeric ratios were found to be >95:5 for all the case studied, as determined by $^1$H NMR spectroscopy and HPLC analysis. [d] $\alpha$-Chloroacetophenone was used instead of $\alpha$-bromoacetophenone. [e] The NHC catalyst **5f** was used. [f] No product was observed in the absence of an NHC catalyst. [g] Reaction time 18 h.

When a *cis*-epoxide (*cis*-**4c**) was subjected to the optimized reaction conditions, it remained a *cis* isomer. Also, the Darzens reaction of the $\alpha$-bromoketone **6a** and **1e** at low temperature (−40 to −10 °C) did not produce the *cis*-epoxy ketone. These results suggest that the reaction is irreversible and the *trans*-product, once formed, is thermodynamically more stable. Kinetic experiments revealed that an NHC-catalyzed Darzens reaction proceeds faster than the formation of the phenacyl bromide under the reaction conditions (see the Supporting Information for details).



*Scheme 3.* NHC-catalyzed enantioselective Darzens reaction.

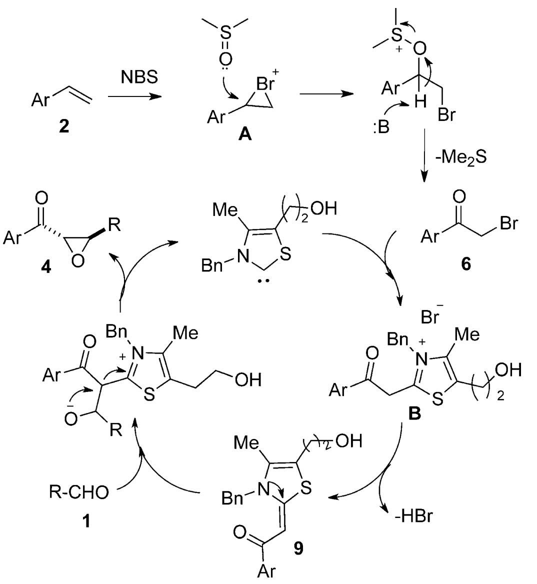
To probe mechanistic details further, the following stoichiometric control experiments were carried out (Scheme 4): a) when **2a** was treated with 1 equivalent of **5e**, in the absence of an aldehyde, under standard reaction conditions, the ketodeoxy Breslow intermediate **9** was isolated[8] in 48% yield. It was also formed (78%) when **6a** was treated with **5e** under basic conditions, irrespective of whether or not aldehyde is present; b) Furthermore, when **9** was treated with **1e** in DMSO, the corresponding epoxy ketone **4e** was isolated in 64% yield. This leads us to believe that NHC preferentially reacts with phenacyl bromide rather than aldehyde under the optimized reaction conditions, although one cannot rule out the possibility of reaction between the aldehyde and NHC, which may be reversible and hence unproductive.



*Scheme 4.* Stoichiometric experiments.

Based on the aforementioned results and previous reports,[9] a probable catalytic cycle for this NHC-catalyzed oxidative functionalization of styrenes is outlined in Scheme 5. To begin with, styrene reacts with NBS to form the bromonium ion **A**, which undergoes regioselective ring opening with DMSO and subsequent Me$_2$S elimination to provide the phenacyl bromide **6**. The NHC then reacts with **6** to form the intermediate salt **B**, which eliminates HBr to give the ketodeoxy Breslow intermediate **9**. Finally, **9** reacts with aldehyde followed by liberation of the NHC catalyst and furnishes the thermodynamically stable *trans*-$\alpha,\beta$-epoxy ketones **4**.

In summary, we have described, for the first time, a novel organocatalytic process in which oxidative coupling of styrenes with aldehydes take place, thus leading to a facile synthesis of the $\alpha,\beta$-epoxy ketones **4a**–**l** in moderate to good yields with excellent d.r. values (>95%). The procedure employs NHC in catalytic amounts (10 mol%) in combination with NBS/DBU/DMSO as the oxidative system. An



*Scheme 5.* Probable catalytic cycle for oxidative coupling of aldehydes with styrenes/α-bromoketones.

unconventional mechanistic course has been proposed based on the isolated ketodeoxy Breslow intermediate **9**. Further, the α,β-epoxy ketones **4** were obtained by the reaction of α-bromoacetophenones with aldehydes (Darzens reaction including its asymmetric version) using an NHC catalyst under mildly basic conditions. The salient features of the methodology are: 1) metal-free synthesis, 2) milder reaction conditions, and 3) functional-group tolerance and excellent regioselectivity.

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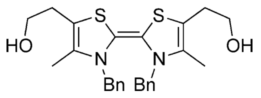

NHC dimer (**8**)

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