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Masked *N*-Heterocyclic Carbene-Catalyzed Alkylation of Phenols with Organic Carbonates

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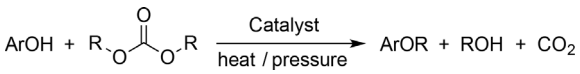
An easily prepared masked *N*-heterocyclic carbene, 1,3-dimethylimidazolium-2-carboxylate (DMI-CO_2), was investigated as a "green" and inexpensive organocatalyst for the alkylation of phenols. The process made use of various low-toxicity and renewable alkylating agents, such as dimethyl- and diethyl carbonate, in a focused microwave reactor. DMI-CO_2 was found to be a very active catalyst and excellent yields of a range of aryl alkyl ethers were obtained under relatively benign conditions. The observed difference in the conversion behavior of phenol methylation, in the presence of either the carbene or 1,8-diazabicycloundec-7-ene (DBU) catalyst, was rationalized on the basis of mechanistic investigations. The primary mode of action for the *N*-heterocyclic carbene is nucleophilic catalysis. Activation of the dialkyl carbonate electrophile results in concomitant evolution of an organo-soluble alkoxide, which deprotonates the phenolic starting material. In contrast, DBU is initially protonated by the phenol and thus consumed. Subsequent regeneration and participation in nucleophilic catalysis only becomes significant after some phenolate alkylation occurs.

The alkylation of phenols to form phenyl alkyl ethers is an important transformation for the synthesis of a wide range of chemical products. Typically, phenyl alkyl ethers are synthesized using harmful alkylating agents, such as alkyl halides and dimethyl sulfate, using the Williamson reaction.[1] Dialkyl carbonates, such as dimethyl carbonate (DMC), have been described as greener, alternative reagents for alkylation (Scheme 1).[2] DMC, for example, is considered a non-toxic, sustainable, biodegradable reagent, and is not classified as a volatile organic compound (VOC) according to the US Environmental Protection Agency. Because DMC can be produced by the catalytic oxidative carbonylation of methanol, the methanol by-product produced under methylation conditions (Scheme 1) can, in principle, be recycled. Examples of alkylation with other dialkyl carbonates, such as diethyl carbonate (DEC) and dibenzyl carbonate (DBnC), are much less prevalent in the literature than are those describing alkylation with DMC.[3] Nevertheless, these longer chain dialkyl carbonates can be readily produced by transesterification of DMC with the corresponding alcohols,[4] as well as by catalytic oxidative carbonylation,[5] opening up the possibility of the synthesis of a wide range of alkyl aryl ethers. One disadvantage of using organic carbonates for the alkylation of phenols is that they are less reactive than other common alkylating agents. Efficient alkylation with DMC, for example, requires the reaction temperature to be considerably higher than the reagent's boiling point (90 °C) and, thus, a high-pressure apparatus is usually required to drive methylation reactions to completion. Moreover, high temperatures, often in conjunction with extended reaction times and an excess amount of a promoter, are required for alkylation with longer chain dialkyl carbonates.[3]

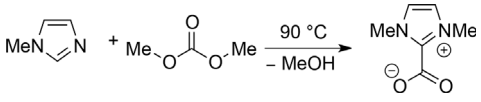


Scheme 1. Catalytic alkylation of phenols with dialkyl carbonates.

Many catalysts have been studied for the alkylation of phenols with DMC and other organic carbonates,[3,6] with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) being one of the most common for this kind of transformation, owing to its high activity and selectivity.[3a,6a–d] It is reported that DBU does not simply act as a base but also as a nucleophilic catalyst that reacts with dialkyl carbonates to generate an intermediate *N*-alkoxycarbonyl-amidinium adduct, which is a strongly activated alkylating agent.[6a] However, DBU is highly toxic,[7] thus an alternative catalyst of potentially lower toxicity, retaining good activity at low cost, is desirable for the construction of a "greener" reaction system.

In numerous transformations *N*-heterocyclic carbenes (NHC) have been utilized extensively as organocatalysts.[8] More specifically, 1,3-dimethylimidazolium-2-carboxylate (DMI-CO_2) is an *N*-heterocyclic carbene precursor (a "masked carbene") that has been employed as a catalyst in the ring-opening polymerization and copolymerization of propylene oxide,[9] and in the synthesis of cyclic carbonates from bio-based diols,[10] including glycerol.[10,11] DMI-CO_2 is attractive, because it can be obtained easily by heating DMC with 1-methylimidazole (Scheme 2),[12] which is itself a less expensive heterocycle than DBU.[13]

Here, we report the investigation of this catalytic system for the alkylation of phenolic compounds, such as guaiacol, syrin-



Scheme 2. Synthesis of DMI-CO_2.

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gol, and cresol derivatives, known to be generated from the depolymerization of lignin.[14] Specifically, the microwave-assisted alkylation of phenolic compounds with organic carbonates catalyzed by the masked carbene, DMI-CO_2, is described in detail.

Using an Ace Glass pressure tube, DMI-CO_2 was synthesized by heating 1-methylimidazole and DMC according to the procedure of Crabtree and co-workers.[12b] Using DMI-CO_2 as a catalyst (10 mol% with respect to the phenolic substrate), phenolic derivatives containing different ring substituents were methylated with DMC in an Anton Paar 300 focused microwave reactor at 160 °C (Table 1).

Table 1. Methylation of different phenolic derivatives with DMC in acetonitrile using DMI-CO_2 as precatalyst.[a]

Entry	Phenolic substrate	Time [min]	Conv. [%]	*O*-methylation product[b] [%]
1	phenol	80	100	100 (71)
2	guaiacol	80	100	99 (95)
3	4-methylguaiacol	80	94	91 (90)
4	syringol	80	99	93 (93)
5	3,5-dimethoxyphenol	80	100	98 (96)
6	*m*-cresol	80	100	99 (84)
7	*p*-cresol	80	99	99 (88)
8	eugenol	80	96	95 (91)
9	vanillin	160	100	74 (77)
10	4-chlorophenol	120	100	100 (94)
11	4-bromophenol	120	100	100 (100)
12	2,6-dichlorophenol	120	100	100 (97)
13	4-benzylphenol	80	100	100 (99)
14	1-naphthol	120	100	100 (99)
15	2-naphthol	120	100	90 (90)

[a] Reaction conditions: phenolic derivatives (2.73 mmol), DMC (3 mL, 13.1 equiv.), acetonitrile (3 mL), and DMI-CO_2 (0.273 mmol; 10 mol% with respect to the phenolic substrate); the reaction mixture was heated at 160 °C in an Anton Paar 300 focused microwave reactor. [b] Yield was quantified by ^{1}H NMR; isolated yield in parentheses; owing to the high volatility of their corresponding products, large discrepancy in yield was observed for Entries 1, 6, and 7.

Most of the investigated phenols were successfully converted to the corresponding methylated products in 91–100% yield after 80 min of heating. Substrates containing electron-withdrawing groups required longer heating times to achieve >90% conversion (4-halophenols and naphthol isomers), affording the desired products with very high selectivity. Vanillin however, was somewhat sluggish to react, requiring 160 min for complete conversion (Entry 9, Table 1), with lower selectivity for the desired product (3,4-dimethoxybenzaldehyde).

Alkylation of phenol with diallyl carbonate (DAC), diethyl carbonate (DEC), and dibenzyl carbonate (DBnC), was also attempted using the masked NHC catalyst. Commercial sources of DEC and DBnC were used; DAC was synthesized by transesterification of DMC with allyl alcohol, in the presence of catalytic amounts of potassium carbonate. Initially, ethylation of phenol with DEC was performed under the standard conditions for methylation, that is, 10 mol% DMI-CO_2, 160 °C, 13.1 equivalent of organic carbonate (Entry 1, Table 2). The reaction resulted in only 15% yield of ethoxybenzene (Conversion: 16%). Catalyst loading and temperature had to be increased for higher conversion rates (Entries 2 and 3, Table 2). Minor amounts of anisole were also detected in the reaction mixture (Entries 1: 0.2%; 2: 1.3%; and 3: 3%). This anisole was probably generated by the *N*-demethylation of the intermediate electrophile as shown below (Scheme 3).

Table 2. Alkylation of phenol with diethyl carbonate, diallyl carbonate, and dibenzyl carbonate in acetonitrile using DMI-CO_2 as precatalyst.[a]

Entry	Carbonate	DMI-CO_2 [mol%]	Conv. [%]	*O*-alkylated product[b] [%]
1	DEC	10	16	15
2	DEC	50	71	70
3[c]	DEC	50	93	90
4	DAC	10	78	78
5[d]	DAC	10	93	93
6	DBnC	10	100	97

[a] Reaction conditions: phenol (2.73 mmol), diethyl carbonate (DEC), diallyl carbonate (DAC), and dibenzyl carbonate (DBnC, 13.1 equiv.) in acetonitrile (3 mL) using DMI-CO_2; the reaction was heated in an Anton Paar 300 focused microwave reactor at 160 °C for 80 min. [b] Yield quantified by ^{1}H NMR. [c] Heated at 170 °C. [d] Heated for 120 min.

Scheme 3. Anisole by-product formation under ethylation conditions.

For DAC, under standard conditions (Entries 4 and 5, Table 2), 77% and 94% of phenol was converted after 80 min (77% yield of allyloxybenzene) and 120 min (93% yield of allyloxybenzene), respectively. Besides allyloxybenzene and trace amounts of anisole (observed using GC–MS, not observable with ^{1}H NMR), no other aromatic products were observed. For DBnC, under standard conditions (Entry 6, Table 2), phenol was fully converted after 80 min to give 97% yield of benzyloxybenzene.

To compare the alkylation activity of DMI-CO_2 versus that of DBU, time-course studies were carried out for the conversion of phenol to anisole with DMC in acetonitrile under similar conditions as experiments reported in in Table 1.

The time-course of DBU-catalyzed methylation of phenol is illustrated in Figure 1. An induction period of approximately 20 min was observed in the presence of 10 mol% (with respect to phenol) DBU. Similar behavior for the DBU-catalyzed esterification of benzoic acid with DMC was described by Shieh and co-workers.[15]

Several factors may contribute to the slow initial rate of methylation in the presence of DBU. The primary cause is likely to be the lack of free DBU available to react with DMC to generate the reactive *N*-methoxycarbonyl amidinium intermediate, that was proposed by Shieh et al. to be the active electrophile (i.e., nucleophilic catalysis).[6a,15] Even before the heating of the

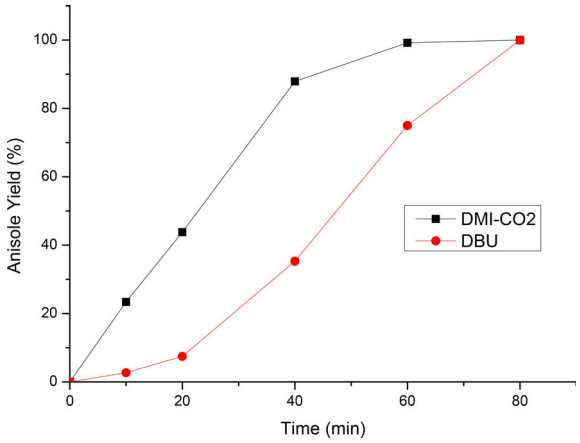


Figure 1. Methylation of phenol (2.73 mmol) with DMC (3 mL, 13.1 equiv.) in acetonitrile (3 mL) using DMI-CO_2 or DBU (0.273 mmol; 10 mol% with respect to phenol) as (pre)catalysts. The reaction mixture was heated at 160 °C in an Anton Paar 300 focused microwave reactor. Yield quantified by ^{1}H NMR.

reaction mixture commenced, the vast majority of DBU would be protonated by the excess phenol in a diffusion-controlled reaction (shown in Figure 2). Furthermore, the cation of the putative intermediate *N*-methoxycarbonyl amidinium methoxide (**1**, R = Me) is expected to be unstable and readily be deprotonated (i.e., by methoxide or another equivalent of DBU) to generate a ketene aminal (**2**), which is known to react with methanol/phenol to regenerate DBU, as well as making DMC or methyl phenyl carbonate (MPC).[16] MPC is expected to be able to react analogously with DBU to generate a *N*-methoxycarbonyl amidinium phenoxide intermediate (**1**, R = Ph).

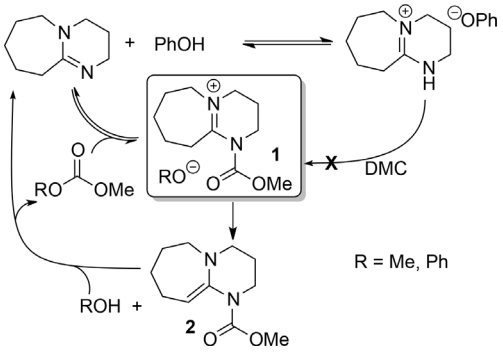


Figure 2. Basic and nucleophilic behavior of DBU.

The subsequent, apparent increase in reaction rate is less straightforward to rationalize. One possibility is that the conversion rate only starts to increase once the initial phenoxide present reacts to produce anisole and methoxide ions. These basic methoxides are then able to either liberate protonated DBU or produce more phenoxide. A proportion of the liberated DBU would then be available to react with DMC, effecting nucleophilic catalysis, increasing the overall methylation rate.

In contrast, the NHC liberated from the pre-catalyst DMI-CO_2 displays very different behavior to DBU (Figure 1). Its initial rate of conversion was considerably faster under analogous conditions: more than 99% of the phenol was converted to anisole after 60 min. No appreciable induction period was observed and a steady increase in the conversion of phenol occurred until the majority of the starting material was consumed. In this case, the pre-catalyst is not initially protonated by phenol and the active carbene catalyst is revealed only upon heating, with evolution of CO_2. Despite the inherent basicity of the NHC (pK_a in DMSO = 21.1)[17] and the presence of phenol, protonation at the C2-position of the NHC would lead to an unstable imidazolium-phenoxide ion-pair, in which equilibrium would favor the carbene.[18] It is well established that NHCs are relatively poor bases but strong nucleophiles,[19] and addition of carbene **3** to dialkyl carbonate, resulting in the highly active 2-alkoxycarbonyl-1,3-dimethylimidazolium electrophile, would account for the observed higher initial reaction rate compared to the DBU case.

A plausible mechanism for this pathway is illustrated in Figure 3. The free NHC catalyst, **3**, which is generated from the decarboxylation of DMI-CO_2, attacks the carbonyl group of dialkyl carbonate at elevated temperature to generate 2-alkoxycarbonyl-1,3-dimethylimidazolium alkoxide **4**. In the studies by Bruijnincx and co-workers,[10] 2-methylcarbonyl-1,3-dimethylimidazolium methoxide could be generated at relatively low temperature (74 °C) from **3** and dimethyl carbonate. The cation of **4** is rationalized as being a more activated alkylating agent than dialkyl carbonate, owing to its positive charge.

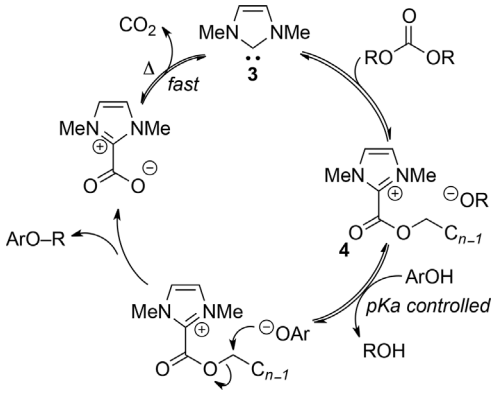
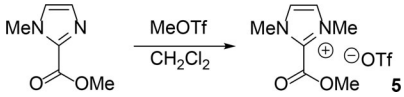


Figure 3. Proposed primary mechanism for the alkylation of phenols with dialkyl carbonates.

To verify this hypothesis the salt 2-methoxycarbonyl-1,3-dimethylimidazolium triflate (**5**) was synthesized (Scheme 4) and reacted with phenol in the presence of the non-nucleophilic base *N*,*N*-diisopropylethylamine (DIPEA).



Scheme 4. Synthesis of 2-methoxycarbonyl-1,3-dimethylimidazolium triflate **5**.

When phenol was heated with **5** in the presence of 1 equivalent of DIPEA for 5 min at 160 °C, anisole and MPC were generated (Entry 1, Table 3). On the contrary, no products were generated when phenol was heated with DIPEA and DMC under analogous conditions (Entry 2, Table 3). To assess the alkylating ability of MPC, a reaction was conducted using it in place of DMC (Entry 3, Table 3). Despite its inherent stability, MPC was able to selectively produce anisole under NHC catalysis (Entry 4, Table 3). This process is proposed to occur through the reactive intermediate 2-methoxycarbonyl-1,3-dimethylimidazolium phenoxide.

Table 3. Mechanistic investigation of phenol methylation.[a]

Entry	Reagent A	Reagent B	Time [min]	Products
1	**5**	DIPEA	5	Anisole, MPC
2	DMC	DIPEA	5	None
3	MPC	DIPEA	5	None
4	MPC	DMI-CO_2	5	Anisole

[a] Reaction conditions: phenol (0.49 mmol), reagents A/B (0.49 mmol), and acetonitrile (2 mL) were heated at 160 °C in an Anton Paar 300 focused microwave reactor.

The alkoxide anion of **4** also plays an important role in the reaction progress, as it is a stronger base than **3** (pK_a values of methanol and ethanol in DMSO are 29.0 and 29.8, respectively)[20] and, hence, the alkoxide can irreversibly deprotonate the phenolic starting material. This phenoxide ion in turn reacts with alkylating agent, **4**, to generate the phenyl alkyl ether product. In the cases where there is a large excess of the dialkyl carbonate and only a small amount of carbene is present, some of the phenoxide may also react directly, albeit slowly, with dialkyl carbonate.

It should be noted that alkoxide is generated continuously after each round of substitution with dialkyl carbonates. The alkoxides would most likely be the strongest base in the reaction mixture and play a major role in the conversion, especially when a small amount of basic catalyst is used. One key attribute of this NHC catalyst is its ability to continuously generate and maintain substantial amounts of soluble alkoxides in the reaction mixture.

In summary, a DMC-derived, masked *N*-heterocyclic carbene (DMI-CO_2) was employed as the catalyst for the alkylation of phenolic derivatives with DMC and other organic carbonates. The NHC arising from the decarboxylation of DMI-CO_2 is very active and selective, as excellent yields of *O*-alkylated products could be generated in short reaction times and under relatively benign conditions. This catalyst is potentially less expensive than DBU, which is the established catalyst for this type of transformation. In this investigation, the different conversion behavior of phenol to anisole, catalyzed by DBU or NHC, was observed and rationalized. The mechanism of the key transformation of this reaction catalyzed by the masked carbene was also proposed: NHC is likely to act as a nucleophilic catalyst, which reacts with the dialkyl carbonate to generate a 2-alkoxycarbonyl-1,3-dimethylimidazolium salt, which is a highly active electrophile for alkylation and an alkoxide base simultaneously, the latter being integral to the successful propagation of the alkylation process.

Experimental Section

Conversion of phenols. A typical procedure for the conversion of phenols with dialkyl carbonate using DMI-CO_2 and DBU as catalysts is as follows: Phenol derivative (2.73 mmol), catalyst, dialkyl carbonate (13.1 equiv.), and acetonitrile (3 mL) were heated in a 30 mL glass tube, fitted with a pressure cap in an Anton Paar Monowave 300 microwave synthesis reactor with a stirring rate of 600 rpm. After heating, the reaction tube was removed from the microwave reactor and cooled to room temperature. Mesitylene (0.2 mL) was then added as an external standard. The solution was then mixed with [D_6]DMSO for ^{1}H NMR analysis. For GC–MS analysis, the sample was passed through a short pad of silica and diluted with acetone before injection.

Isolation of *O*-methylation products. Phenol substrate (2.73 mmol), DMI-CO_2 (0.273 mmol), DMC (3 mL), and acetonitrile (3 mL) were heated in a 30 mL glass tube, fitted with a pressure cap in an Anton Paar Monowave 300 microwave synthesis reactor, with a stirring rate of 600 rpm. After cooling to room temperature, the mixture was concentrated in vacuo. Purification by flash chromatography, eluting with 0–30% ethyl acetate/hexane or diethyl ether/pentane (gradient), afforded the desired product.

Synthesis of DMI-CO_2.[12b] A screw-top 30 mL Ace pressure tube was charged with dimethyl carbonate (9 mL), 1-methylimidazole (6 mL), and a stirrer bar. The mixture was heated for 72 hours at 90 °C. The solid was filtered and was washed thoroughly with methylene chloride (3×40 mL), acetone (3×40 mL), and diethyl ether (3×40 mL). The yield of solid DMI-CO_2 was 8.2 g (78%). ^{1}H NMR (D_2O): $\delta = 7.30$ (2H, s, 2×*CH*N), 3.92 ppm (6H, 2×*CH*$_3$N); ^{13}C NMR (D_2O, ext. std. CH_3OH): $\delta = 158.5$ (CO_2), 140.1 (*C*CO_2), 123.4 (2×*C*HN), 37.1 ppm (2×*C*H$_3$N).

Synthesis of diallyl carbonate. A mixture of allyl alcohol (80 mL, 1.18 mol), dimethyl carbonate (20 mL, 0.24 mol), and potassium carbonate (7.7 g, 55.7 mmol) were stirred at 70 °C for 6 h in a round-bottomed flask. Then the reaction mixture was concentrated slowly in vacuo at 60 °C under reducing pressure. The solid was then filtered and washed with dichloromethane (100 mL). The organic solution was then extracted with distilled water (2×10 mL) and concentrated in vacuo to give diallyl carbonate as a colorless liquid (18 g, 53%). ^{1}H NMR ($CDCl_3$): $\delta = 5.95$ (2H, ddt, $J = 17.2$, 10.6, 5.5 Hz, 2×CH$_2$=*CH*), 5.23–5.42 (4H, m, 2×*CH*$_2$=CH), 4.64 ppm (4H, d, $J = 5.7$ Hz, *CH*$_2$O); ^{13}C NMR ($CDCl_3$): $\delta = 155.0$ (OCO_2), 131.7 (CH*C*H$_2$OCO$_2$), 119.0 (*C*H$_2$CHCH$_2$OCO$_2$), 68.6 ppm (CH$_2$*O*CO$_2$).

Synthesis of 5.[21] To a solution of methyl 1-methylimidazole-2-carboxylate (1.6 g, 11.4 mmol) in dried dichloromethane (100 mL) was added neat methyl triflate (1.2 mL) dropwise at room temperature under nitrogen. After stirring for 18 h, the solution was concentrated by rotary evaporation of the solvent and the resulting white solid was recrystallized with acetone/diethyl ether mixture to give the pure product (2.9 g, 84%). ^{1}H NMR (D_2O): $\delta = 7.55$ (2H, s, *CH*$_2$N), 4.04 (6H, s, 2×NC*H*$_3$), 4.02 ppm (3H, s, OC*H*$_3$); ^{13}C NMR (D_2O, ext. std. CF_3COOH): $\delta = 157.4$ (*C*OOCH$_3$), 134.9 (*C*COOCH$_3$), 128.4 (2×*C*HN), 122.0 (q, 317 Hz, SO_3CF_3), 56.4 (COO*C*H$_3$), 40.9 ppm (2×*C*H$_3$N); ^{19}F NMR (D_2O, ext. std. CF_3COOH): −79.6.

Synthesis of MPC. Diphenyl carbonate (3 g, 14.0 mmol), methanol (4.5 g, 140 mmol), and acetonitrile (5 mL) were heated in the microwave reactor for 100 min. The volatile materials were removed on a rotary evaporator to give a crude mixture, which was separated on silica gel using hexane/diethyl ether (85:15) as eluent to give pure methyl phenyl carbonate (0.85 g, 40%). ^{1}H NMR ($CDCl_3$): $\delta = 7.39$ (2H, app t, $J = 7.5$ Hz, $C_{3,5}$-*H*), 7.14–7.29 (3H, m, $C_{2,4,6}$-*H*), 3.90 ppm (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 154.4$ (*C*=*O*), 151.3 (C_1), 129.6 (C_3 and C_5), 126.2 (C_4), 121,2 (C_2 and C_6), 55.5 ppm (CH_3); GC-MS: *m/z* 152 (M^+, 49%), 108 (39), 93 (19), 78 (100), 65 (92).

Synthesis of allyloxybenzene. Allyloxybenzene was synthesized following a procedure[22] reported previously. The compound was used to verify the product of alkylation of phenol with diallyl carbonate (Entries 4 and 5, Table 2). ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.28$ (2H, app t, $J = 7.1$ Hz, $C_{3,5}$-*H*), 6.89–6.99 (3H, m, $C_{2,4,6}$-*H*), 5.96–6.13 (1H, m, $ArOCH_2CH$), 5.39 (1H, d, 17.3 Hz, $ArOCH_2CHCH_2$), 5.25 (1H, d, 10.3 Hz, $ArOCH_2CHCH_2$), 4.52–4.58 ppm (1H, m, $ArOCH_2CHCH_2$); GC-MS: *m/z* 134 (M^+, 100%), 119 (42), 105 (15), 94 (57), 77 (27), 65 (38), 51 (30).

Synthesis of benzyloxybenzene. Benzyloxybenzene was synthesized following a procedure[23] reported previously. The compound was used to verify the product of alkylation of phenol with dibenzyl carbonate (Entry 6, Table 2). ^{1}H NMR ([D$_6$]DMSO): $\delta = 7.24$–7.49 (7H, m, other Ar-*H*), 7.01 (2H, d, 7.5 Hz, $C_{2,6}$-*H*), 6.94 (1H, 7.4 Hz, C_4-*H*), 5.10 ppm (3H, s, OCH_2); GC-MS: *m/z* 184 (M^+, 9%), 91 (100), 65 (17).

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Keywords: alkylation · carbenes · lignin · organic carbonates · organocatalysis

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[13] Comparing the prices of samples from Sigma–Aldrich: 38 Australian Dollars per mole for 1-methylimidazole and 148 Australian Dollars per mole for DBU (both based on 500 g pack size). In addition, LD50 Oral—Rat of 1-methylimidazole is 1144 mg kg^{-1} (Safety Data Sheet from Sigma–Aldrich), a significantly higher value than for DBU: see ref. [7]).

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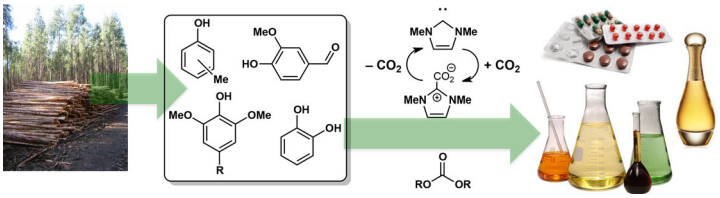
Masked *N*-Heterocyclic Carbene-Catalyzed Alkylation of Phenols with Organic Carbonates



The masked carbene: Organic carbonates including dimethyl- and diethyl carbonate are safer, renewable, but less reactive alkylating agents than alkyl halides or sulfates. We unmask an *N*-heterocyclic carbene for the catalyzed alkylation of phenols, many of which can be derived from lignin, with these organic carbonates. The resulting aryl alkyl ethers are important for use in the flavor, fragrance, and pharmaceutical industries.