Mild and Efficient Iodine-Catalyzed Direct Substitution of Hydroxy Group of Alcohols with C- and N-Nucleophiles

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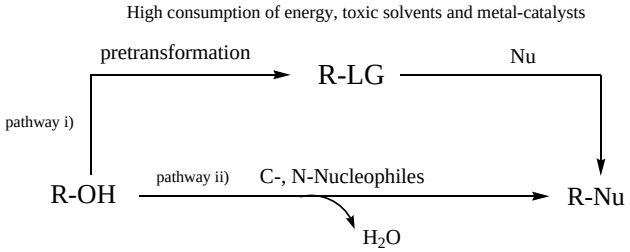
Abstract: A mild and efficient iodine-catalyzed direct substitution of hydroxy group of allylic, progargylic and other alcohols with various C- and N-nucleophiles was described in this contribution. C-C and C-N bond formations could be readily achieved by non-metallic and green catalysis for various compounds. This facilitates access to possible transformations of a broad scope of substrates into bioactive and pharmaceutically important building blocks.

Keywords: Allylation, Bond formation, C-, N-nucleophiles, Green chemistry, Iodine, Isomerization, Propargylation, Substitution.

C-C and C-N bond formation reactions [1] have attracted tremendous attention and have been widely studied in synthetic organic chemistry since they provide access to various biologically active intermediates and pharmaceutically important molecules. The set-up of direct substitution protocols employing general alcohols with C- and N-nucleophiles is desirable from the point of view of atom economy [2] and green chemistry [3]. However, traditional strategies have some limitations in that hydroxy group in alcohols is generally pretransformed into other leaving groups which could be easily removed, such as acetates, carbonates, halides etc. These unnecessary pretransformations not only bring about high consumption of energy, toxic organic solvents and precious transition-metal or rare earth catalysts, but also result in operational complexity and low efficiency in multistep conversions (pathway i, Scheme **1**). In contrast, direct C-C and C-N bond formation reactions of alcohols with aromatic or aliphatic nucleophiles are greener and more economical synthetic methodologies in which environmentally benign water is the only byproduct and can be discarded to circumstances without any pollution. There is no need to input plenty of preactivators, energy and chemicals, and catalytic C-X bond formations can be achieved in one step (pathway ii, Scheme **1**). In this context, developing new, mild and efficient strategies for direct substitution of hydroxy groups in alcohols with aromatic or aliphatic nucleophiles rekindles chemist's interests due to the above-mentioned advantages.

Nowadays, various transition-metal complexes or metal Lewis acids, are precious, air/moisture-sensitive and difficult to handle, they have been widely used to catalyze the allylic, propargylic substitutions and other alkylations with C- and N-nucleophiles [4]. In some cases, additives are also indispensable as copromoters and excessive amine nucleophiles are often necessary for smooth completion in



Scheme 1. Direct substitution of hydroxy groups in alcohols *vs*. multistep transformations.

propargylic substitutions of amides [4a-c]. Since the leaving ability of hydroxy group is not satisfactory under mild conditions, high reaction temperature is often required. Although the alkylation of indoles [4d-p], amines and amides [4q-u] has been studied by Bandini, Ishimura and other groups, unsatisfactory regioselectivity and narrow substrate scope are limitations for further practical applications.

In recent years, iodine has emerged as a versatile Lewis acid catalyst for various organic transformations such as Michael addition [5a-c], coupling [5d], cycloaddition [5e], silylation [5f], protection/deprotection [5g-j] and even multi-component synthesis [5k-n], in which it can efficiently activate C=C, C=O, C=N and other functional groups. Iodine is a cheap and commercially available catalyst with high tolerance to air and moisture. As an extension of our previous work [5o], we intend to describe the iodine-catalyzed direct substitution of alcohols with C- and N-nucleophiles to elucidate a more efficient allylation, propargylation and other alkylation protocols with a versatile substrate scope under mild reaction conditions.

Initially, allylation reaction of indoles with E-1,3-diphenyl-2-propen-1-ol **1a** was selected as model reaction to investigate the iodine-catalyzed direct substitution and the substrate scope (Fig. **1**). Excellent yield of desired product 3-((E)-1,3-diphenylallyl)-1*H*-indole **3a** was afforded when indole

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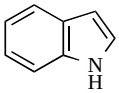
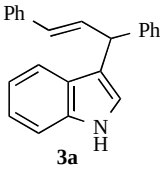
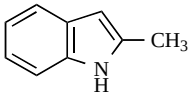
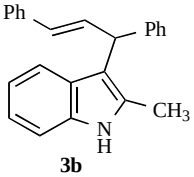
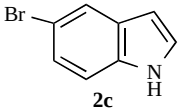
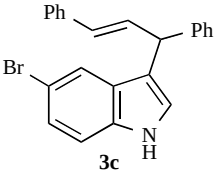
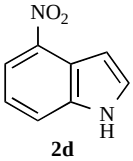
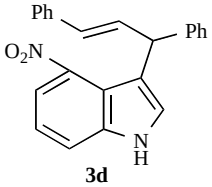
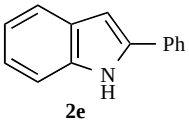
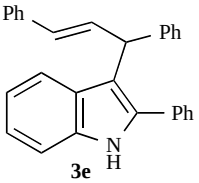
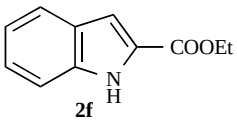
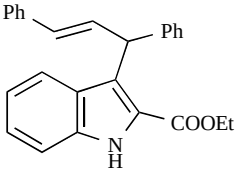
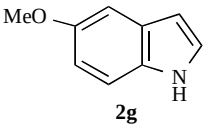
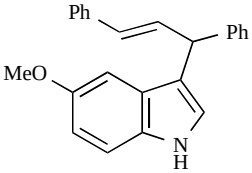
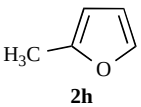
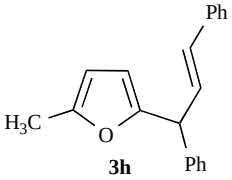
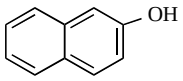
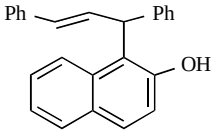
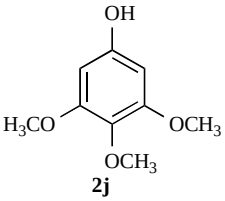
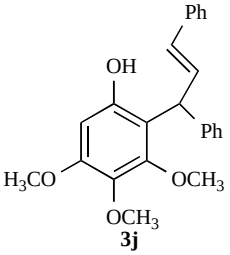
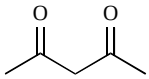
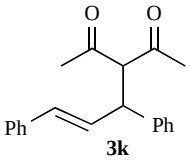
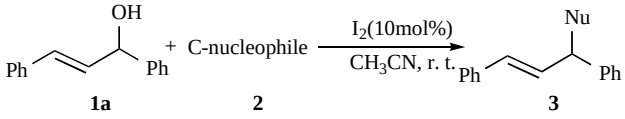
Table 1. Iodine-Catalyzed Allylation of C-Nucleophiles

Entry	C-nucleophile	Time(h)	Product	Yield%
1	 **2a**	7	 **3a**	92
2	 **2b**	12	 **3b**	93
3	 **2c**	10	 **3c**	92
4	 **2d**	6.5	 **3d**	93
5	 **2e**	7	 **3e**	95
6	 **2f**	10	 **3f**	91
7	 **2g**	10	 **3g**	80
8	 **2h**	6	 **3h**	82

(Table 1). Contd…..

Entry	C-nucleophile	Time(h)	Product	Yield%
9	 **2i**	10	 **3i**	91
10	 **2j**	12	 **3j**	79
11	 **2k**	10	 **3k**	95



1a **2** **3**

Fig. (1).

2a was reacted in acetonitrile at room temperature under the catalysis of 10mol% molecular iodine (Entry 1, Table **1**). Encouraged by this result, various indoles were reacted in this substitution and corresponding 3-allylated products were given in excellent yields (Entry 2-7). The direct allylation was satisfactory for both electron-rich and electron-deficient indole substrates. Furthermore, this efficient protocol was expanded to other aromatic compounds 2-methyl furan and phenols, the expected allylated products were yielded regioselectively and smoothly under the optimized conditions (Entry 8-10). The aliphatic nucleophile pentane-2,4-dione **2k** could also be converted into **3k** in 95% yield (Entry 11).

Besides of C-nucleophiles, a variety of amides, such as sulfonamides, carboxamides and carbamates, which are less nucleophilic, were then investigated in this direct substitution reaction (Fig. **2**, Table **2**). It was found that most amides screened could be efficiently transformed to give N-allylated compounds excellent yields. p-Nitrobenzenesulfonamide and benzamide were less reactive and only moderate yield were afforded (Entry 2, 5). These reactions were cleanly achieved to give the expected products without the employment of transition-metal catalyst, additives or harsh reaction conditions, which overran the Pd-catalyzed[4r,s] or $Bi(OTf)_3/KPF_6$ [4v] protocols. Nevertheless, since the allylic amination requires more activation energy at high temperature [4q], both nicotinamide and p-toluidine remained intact after prolonged stirring with **1a** and starting materials were recovered under such mild condition (Entry 8, 9).

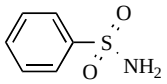
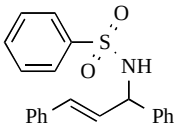
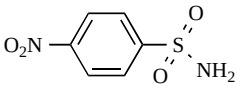
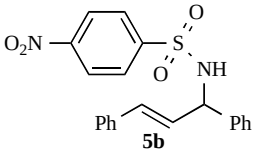
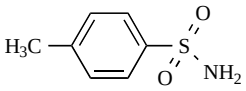
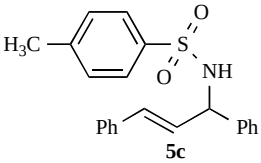
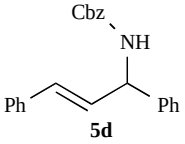
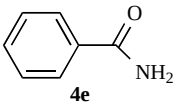
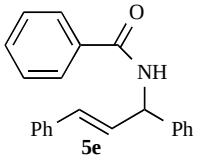
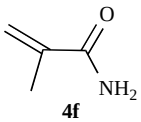
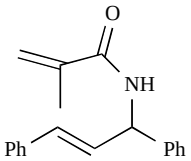
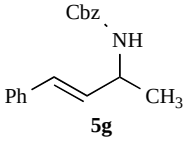
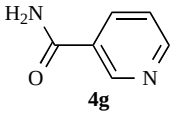
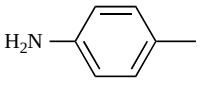
To further expand the substrate scope in this direct substitution methodology, more alcohols with varied nucleophiles were screened (Fig. **3**). Propargylic alcohol **1c**, which is inert or less reactive than allylic counterparts, was reacted with indoles and amides to achieve good yields and smooth propargylation (Table **3**).

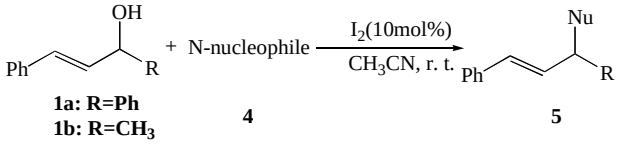
As shown in Fig. (**4**), Triphenylmethanol **1d** was also an effective alkylating agent which could produce 3-(triphenylmethyl)-1*H*-indoles **7a**, **7b** in several minutes and excellent yields (Entry 1 and 2, Table **4**). However, no desired N-(triphenylmethyl)carbamate was produced due to lower nucleophilicity of benzyl carbamate **4d** (Entry 3). To our delight, direct and efficient substitution of electron-deficient Baylis-Hillman alcohols [4f, 6] **1e**, **1f** with 2-methyl-1*H*-indole **2b** and trimethoxybenzene **2l** could be accomplished to give the corresponding alkylation products in reasonable yields (Entry 4, 5).

o-Allylic and o-propargylic phenols have been reported in base-promoted cyclization for synthesis of 5-exo benzofuran or 6-endo benzopyran derivatives [7]. We hypothesized that this cyclization might be achieved using our allylated phenols **3i** and **3j** under basic conditions (1equiv. of KOBu-t/CH_3CN). To our surprise, isomerized products, i. e. o-alkenyl phenols **8a** and **8b** (instead of 6-endo chromene or 5-exo 2,3-dihydrobenzofuran) were afforded at room temperature which indicate a mild base-assisted double bond migration [8] occurred to give a more conjugated and stable aromatic system (Scheme **2**).

In conclusion, we have described an efficient iodine-catalyzed direct substitution of hydroxy group of allylic, progargylic and other alcohols with various C- and N-nucleophiles under mild conditions [9]. Further studies on

Table 2. Iodine-Catalyzed Allylation of N-Nucleophiles

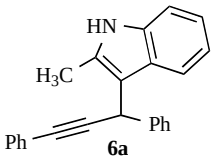
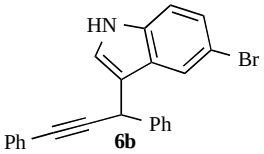
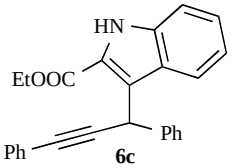
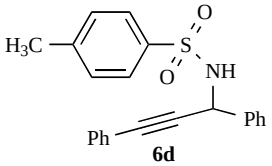
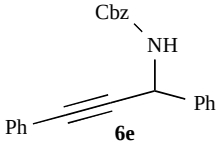
Entry	N-nucleophile	Allylic alcohol	Time(h)	Product	Yield%
1	 **4a**	**1a**	12	 **5a**	86
2	 **4b**	**1a**	14	 **5b**	46
3	 **4c**	**1a**	13	 **5c**	74
4	 **4d**	**1a**	14	 **5d**	94
5	 **4e**	**1a**	13	 **5e**	43
6	 **4f**	**1a**	14	 **5f**	91
7	**4d**	**1b**	9	 **5g**	96
8	 **4g**	**1a**	14	—	n.r.
9	 **4h**	**1a**	20	—	n.r.

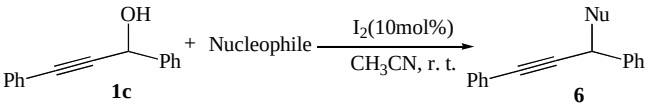


1a: R=Ph **1b: R=CH_3** **4** **5**

Fig. (2).

Table 3. Iodine-Catalyzed Propargylation of C- and N-Nucleophiles

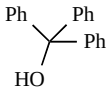
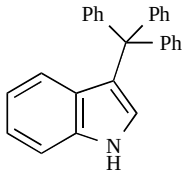
Entry	Nucleophile	Time(h)	Product	Yield%
1	**2b**	20	 **6a**	33
2	**2c**	20	 **6b**	81
3	**2f**	12	 **6c**	87
4	**4c**	36	 **6d**	84
5	**4d**	36	 **6e**	78



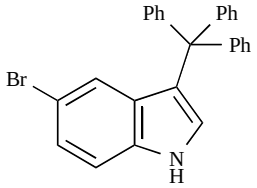
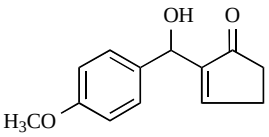
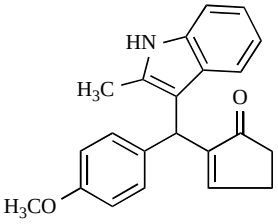
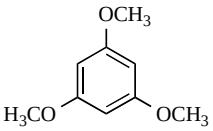
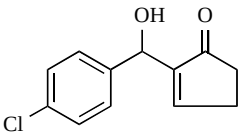
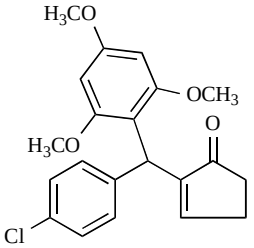
1c **6**

Fig. (3).

Table 4. Iodine-Catalyzed Direct Substitution of Alcohols

Entry	Nucleophile	Alcohol	Time(h)	Product	Yield%
1	**2a**	 **1d**	0.75	 **7a**	98

(Table 4). Contd…..

Entry	Nucleophile	Alcohol	Time(h)	Product	Yield%
2	**2c**	**1d**	1	 **7b**	86
3	**4d**	**1d**	12	—	n.r.
4	**2b**	 **1e**	2	 **7c**	90
5	 **2l**	 **1f**	20	 **7d**	61

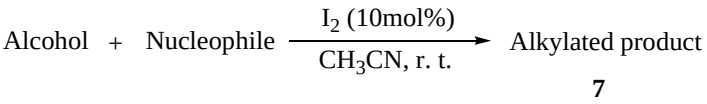
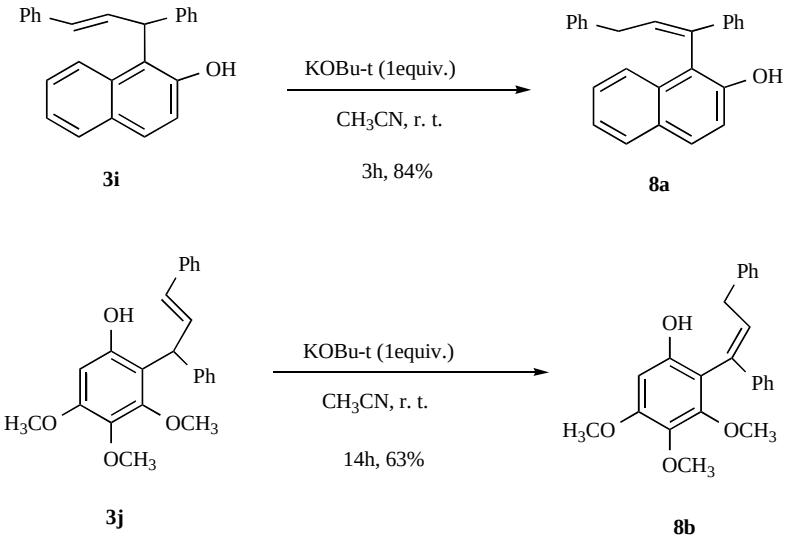


Fig. (4).



Scheme 2. t-BuOK-assisted isomerization of allylated phenols.

extension of substrate scope, detailed mechanism and practical applications are underway in our laboratories.

ACKNOWLEDGEMENTS

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[9] Representative experimental procedure:
Methacrylamide **4f** (48 mg, 0.56 mmol) and E-1,3-diphenyl-2-propen-1-ol **1a** (119 mg, 0.57 mmol) were added into a flask at room temperature. Acetonitrile (15 ml) was then poured and the resulting mixture was vigorously stirred. Molecular iodine (14.4 mg, 0.057 mmol) was added and the mixture was stirred for 14 hours, monitored by TLC. After the completion of reactions, saturated solution of $Na_2S_2O_3$ (2×5 ml) was poured, followed by the addition of water and ether (3×5 ml) to extract the crude product. Organic solvents were combined, dried by anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash chromatography to afford clean product **5f** as a pale yellow solid (144 mg, yield= 91%).
Spectrum data for unknown compounds:
3h: Yellow oil. ^{1}HNMR (300MHz, $CDCl_3$):δ 2.34(s, 3H) 4.93(d, J=7.3Hz, 1H) 5.98(d, J=2.0Hz, 1H) 6.05(d, J=2.0Hz, 1H) 6.48(d, J=15.9Hz, 1H) 6.65(dd, J=15.9Hz, 1H) 7.28-7.46(m, 10H). ^{13}CNMR (75MHz, $CDCl_3$):δ 13.7, 48.5, 106.1, 107.6, 126.5, 126.9, 127.5, 128.4, 128.5, 128.6, 130.2, 131.5, 137.2, 141.5, 151.5, 154.3. IR (film): 3059, 3027, 1599, 1218, 965, 745, 697 cm^{-1}. Mass: *m/z* calcd. for $C_{20}H_{18}O$: 274.1400, found 274.1355.
3j: Colorless liquid. ^{1}HNMR (300MHz, $CDCl_3$):δ 3.71(s, 3H) 3.72(s, 3H) 3.81(s, 3H) 5.36(s, 1H) 5.45(d, J=7.0Hz, 1H) 6.21(s, 1H) 6.47(d, J=15.8Hz, 1H) 6.84(dd, J=15.8Hz, 1H) 7.15-7.39 (m, 9H). ^{13}CNMR (75MHz, $CDCl_3$):δ 43.7, 55.9, 61.1, 61.2, 97.3, 115.1, 126.5, 126.6, 127.5, 127.9, 128.6, 128.7, 130.7, 132.3, 136.4, 137.2, 142.6, 150.7, 152.2, 152.8. IR (film): 3410, 3058, 2938, 1603, 1460, 1199, 1127, 910, 732, 697 cm^{-1}. Mass: *m/z* calcd. for $C_{24}H_{24}O_4$: 376.1675, found 376.1678.
5f: Pale yellow solid, mp. 119-121°C. ^{1}HNMR (300MHz,$CDCl_3$):δ 1.96(s, 3H) 5.33(s, 1H) 5.73(s, 1H) 5.84(t, J=7.1Hz, 1H) 6.35(dd, J=15.9Hz, 1H) 6.42(d, J=7.9Hz, 1H) 6.52(d, J=15.9Hz, 1H) 7.18-7.36(m, 10H). ^{13}CNMR (75MHz,$CDCl_3$):δ 18.8, 54.9, 119.8, 126.6, 127.2, 127.7, 127.9, 128.6, 128.9, 128.9, 131.7, 136.5, 140.1, 141.0, 167.5. IR (KBr): 3304, 3060, 3028, 1654, 1616, 1523, 1210, 967, 746, 696 cm^{-1}. Mass: *m/z* calcd. for $C_{19}H_{19}NO$: 277.1467, found 277.1469.
7b: Pale white solid, mp. 180-182°C. ^{1}HNMR (300MHz, $CDCl_3$):δ 6.75(s, 1H) 6.83(s, 1H) 7.15-7.24(m, 17H) 7.92(s, 1H). ^{13}CNMR (75MHz, $CDCl_3$):δ 59.3, 112.4, 112.6, 123.8, 124.8, 125.1, 126.2, 126.5, 127.5, 129.6, 130.7, 135.6, 146.1. IR (KBr): 3436, 3022, 1442, 1108, 905, 731, 699 cm^{-1}. Mass: *m/z* calcd. for $C_{27}H_{20}NBr$: 437.0779, found 437.0776.
7c: Brown liquid. ^{1}HNMR (300MHz, $CDCl_3$):δ 2.23(s, 3H) 2.39-2.57(m, 4H) 3.73(s, 3H) 5.30(s, 1H) 6.76(d, J=7.8Hz, 2H) 6.92(t, J=7.5Hz, 1H) 7.00-7.22(m, 5H) 7.29(s, 1H) 8.01(s, 1H). ^{13}CNMR (75MHz, $CDCl_3$):δ 12.1, 26.4, 34.9, 37.2, 55.2, 110.5, 111.4, 113.6, 119.0, 119.2, 120.6, 127.9, 129.3, 132.5, 134.0, 135.4, 148.9, 157.9, 159.8, 208.9. IR (film): 3392, 3011, 2922, 1694, 1246, 1036, 752 cm^{-1}. Mass: *m/z* calcd. for $C_{22}H_{21}NO_2$: 331.1572, found 331.1568.
7d: Yellow oil. ^{1}HNMR (300MHz, $CDCl_3$):δ 2.35-2.66(m, 4H) 3.63(s, 6H) 3.77(s, 3H) 5.58(s, 1H) 6.12(s, 2H) 7.01-7.25(m, 5H). ^{13}CNMR (75MHz, $CDCl_3$):δ 24.1, 32.5, 33.5, 52.9, 53.3, 89.1, 108.9, 125.3, 127.2, 128.6, 138.9, 144.7, 156.5, 157.7, 157.8, 206.2. IR (film): 3004, 2936, 1700, 1461, 1114, 818, 752 cm^{-1}. Mass: *m/z* calcd. for $C_{21}H_{21}ClO_4$: 372.1128, found 372.1131.
8a: Colorless oil. ^{1}HNMR (300MHz, $CDCl_3$):δ 3.17(d, J=7.3Hz, 2H) 5.29(s, 1H) 6.77(t, 1H) 6.98-7.75(m, 16H). ^{13}CNMR (75MHz, $CDCl_3$):δ 36.5, 117.3, 117.7, 123.5, 124.7, 126.2, 126.8, 127.9, 128.3, 128.6, 128.7, 129.2, 129.9, 132.9, 133.8, 139.3, 139.8, 150.5. IR (film): 3506, 3058, 3028, 2922, 1594, 1195, 815, 754, 698 cm^{-1}. Mass: *m/z* calcd. for $C_{25}H_{20}O$: 336.1514, found 336.1522.
8b: Colorless liquid. ^{1}HNMR (300MHz, $CDCl_3$):δ 3.40(t, J=9.6Hz, 2H) 3.55(s, 3H) 3.81(s, 3H) 3.89(s, 3H) 4.99(s, 1H) 6.42(s, 1H) 6.58(t, J=9.6Hz, 1H) 7.18-7.32(m, 10H). ^{13}CNMR (75MHz, $CDCl_3$):δ 36.4, 55.9, 60.7, 61.0, 94.9, 111.4, 126.2, 127.6, 128.4, 128.5, 128.6, 132.6, 133.0, 136.3, 139.9, 140.5, 149.1, 151.7, 154.1. IR (film): 3439, 3058, 2936, 1607, 1491, 1458, 1232, 1125, 1031, 757, 698 cm^{-1}. Mass: *m/z* calcd. for $C_{24}H_{24}O_4$: 376.1675, found 376.1678.