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Synthesis of Allylbenzene Derivatives through sp^3 C–H Bond Functionalization of Toluene Derivatives

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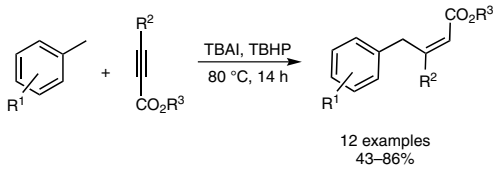

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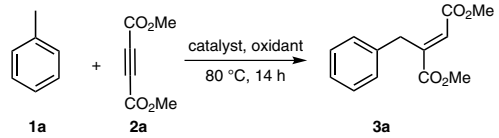
Abstract An sp^3 C–H bond-transformation reaction of toluene substrates to afford the corresponding allylbenzene derivatives is described. Optimum conditions were identified as involving the use of tetrabutylammonium iodide and *tert*-butyl hydroperoxide at 80 °C.

Keywords C–H activation, methylarenes, C–C bond formation, alkyl arylalkenoates, alkynes

Although C–H bonds are generally unreactive, transition-metal-catalyzed C–H bond activation provides an opportunity to convert nonactivated C–H bonds into carbon–heteroatom or carbon–carbon bonds.[1–8] Methods based on this type of reaction have profoundly altered the range of protocols available for the construction of organic compounds and permit the preparation of functionalized compounds from simple starting materials. Regardless of their history,[9,10] conversions of this type still attract attention. Allylbenzenes are usually prepared by the reaction of aryl Grignard reagents with allyl bromides or through metal-catalyzed cross-coupling reactions.[11–14] Fujiwara and co-workers reported a reaction between aromatic substrates and alkynes to form styrene derivatives.[15] Subsequently, Zhang and co-workers developed an sp^3 C–H activation reaction for the benzylation of carboxylic acids with toluene as the benzyl source.[16] They also reported that tetrabutylammonium iodide and *tert*-butyl hydroperoxide permit the benzylation of aromatic carboxylic acids with toluene.[17] Recently, the Maruoka group has developed a concise metal-free C–H bond-functionalization reaction of alkylbenzenes with hypervalent iodine(III).[18] Because of the prominence of C–H functionalization in organic synthesis, and in continuation of our research interest in catalysis,[19–21] we were inspired to explore a strategy for preparing allylbenzenes by a reaction involving toluene and alkynes.

We initially examined the coupling of toluene (**1a**) with dimethyl but-2-ynedioate (**2a**) in the presence of tetrabutylammonium iodide (TBAI) as a model reaction to assess the reaction efficiency. Stirring these reactants at 80 °C for 14 hours in the presence of iodosobenzene diacetate [$PhI(OAc)_2$] as an oxidant afforded dimethyl 2-benzylfumarate (**3a**) in 34% yield, together with benzyl acetate as a by-product in 15% yield. Selected results from our screening experiments are summarized in Table 1. No reaction took place in the absence of a catalyst, even at an elevated temperature (Table 1, entry 15). Only a trace of fumarate **3a** was obtained in the absence of an oxidant source (entry 16). The effects of various oxidants on the progress of the reaction were assessed (entries 1–10). Among the oxidants examined, the best results were obtained by using *tert*-butyl hydroperoxide (TBHP), which gave fumarate **3a** in 84% yield (entry 1). Common inorganic oxidants such as NaClO, H_2O_2, $K_2S_2O_8$, or dioxygen completely inhibited the reaction (entries 2–4). However, a modest increase in yield occurred when DDQ was used as the oxidant, whereas 1,4-benzoquinone was less effective (entries 6 and 7). No reaction took place when di-*tert*-butyl peroxide (DTBH) was used as the oxidant (entry 8). When the reaction was performed in the presence of iodosobenzene bis(trifluoroacetate), enedioate **3a** was isolated in moderate yield (entry 10). Surprisingly the commonly used C–H activation catalyst system $Pd(TFA)_2/O_2$ gave only a low yield of the product (entry 11), whereas tetraethylphosphonium iodide (TEPI) gave a 43% yield of **3a** (entry 12). Note that when the reaction was conducted with 1.0 mmol of **1a**, only traces of the desired product were formed (entry 17).

Table 1 Optimization of the Reaction Conditions[a]



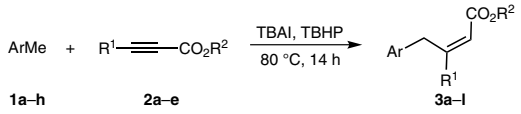
1a 2a 3a

Entry	Catalyst	Oxidant	Yield (%)
1	Bu_4NI	TBHP	84
2	Bu_4NI	O_2	–
3	Bu_4NI	NaClO	–
4	Bu_4NI	$K_2S_2O_8$	–
5	Bu_4NI	H_2O_2	–
6	Bu_4NI	DDQ	39
7	Bu_4NI	BQ	–
8	Bu_4NI	DTBH	–
9	Bu_4NI	$PhI(OAc)_2$	34
10	Bu_4NI	$PhI(TFA)_2$	59
11[b]	$Pd(TFA)_2$	O_2	27
12	TEPI	TBHP	43
13	Bu_4NCl	TBHP	–
14	Bu_4NBr	TBHP	–
15	–	TBHP	–
16	Bu_4NI	–	–
17[c]	Bu_4NI	TBHP	13

[a] Reaction conditions: **1a** (1.5 mL), **2a** (1.0 mmol), catalyst (20 mol%), oxidant (2.0 mmol), 80 °C, 14 h.
[b] Reaction conditions: **1a** (1.0 mL), **2a** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), O_2 (1 atm), DMF (1 mL), TfOH (0.2 mmol), 130 °C, 14 h.
[c] Reaction conducted with 1.0 mmol of **1a**.

Having determined the optimum reaction conditions (Table 1, entry 1), we explored the scope of the reaction (Table 2).[22] We found that toluene derivatives possessing a wide range of functional groups reacted in moderate to high yields. Products containing chloro or bromo substituents were obtained in good yields (entries 2 and 3), and this tolerance of halide functionality on the aromatic ring offers an opportunity for subsequent cross-coupling reactions. Reactions conducted with 4- or 2-methoxy substituted toluenes **1d** and **1e** gave good yields of the corresponding products (entries 4 and 5), whereas the presence of a hydroxy group was not compatible with this reaction (not shown). Electron-deficient substrates such as **1f** and **1g** gave low yields of the corresponding products (entries 6 and 7). 1-Methylnaphthalene (**1h**) gave the desired product in high yield (entry 8). Reactions conducted with other electron-deficient alkynes were also successful (entries 9–11). Note that the reaction conducted with methyl propiolate (**2e**) resulted in a lower yield than did the reactions of internal alkynes, probably due to interference by the acetylenic hydrogen (entry 12).

Table 2 Reaction Scope for Direct Transformation of the sp^3 C–H of Toluene Derivatives[a]

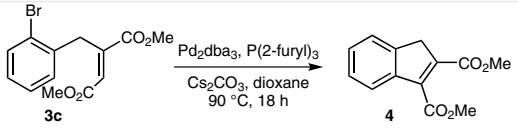


1a–h 2a–e 3a–l

Entry	Toluene	Ar	Alkyne	R^1	R^2	Product	Yield (%)
1	**1a**	Ph	**2a**	CO_2Me	Me	**3a**	84
2	**1b**	4-ClC_6H_4	**2a**	CO_2Me	Me	**3b**	86
3	**1c**	2-BrC_6H_4	**2a**	CO_2Me	Me	**3c**	78
4	**1d**	4-$MeOC_6H_4$	**2a**	CO_2Me	Me	**3d**	86
5	**1e**	2-$MeOC_6H_4$	**2a**	CO_2Me	Me	**3e**	81
6	**1f**	2-$O_2NC_6H_4$	**2a**	CO_2Me	Me	**3f**	62
7	**1g**	3-NCC_6H_4	**2a**	CO_2Me	Me	**3g**	71
8	**1h**	1-naphthyl	**2a**	CO_2Me	Me	**3h**	86
9	**1a**	Ph	**2b**	CO_2Et	Et	**3i**	83
10	**1a**	Ph	**2c**	Ph	Me	**3j**	80
11	**1a**	Ph	**2d**	Me	Me	**3k**	76
12	**1a**	Ph	**2e**	H	Me	**3l**	43

[a] Reaction conditions: **1** (1.5 mL), **2** (1.0 mmol), TBAI (20 mol%), TBHP (2.0 mmol), 80 °C, 14 h.

To explore the synthetic utility of the adducts for conversion into indene derivatives, we treated product **3c** with $Pd_2(dba)_3$ and tris(2-furyl)phosphine in 1,4-dioxane. After 18 hours, dimethyl 1*H*-indene-2,3-dicarboxylate (**4**) was formed in 89% yield (Scheme 1).



3c 4

Scheme 1 Formation of dimethyl 1*H*-indene-2,3-dicarboxylate

In conclusion, we have developed a catalytic system for the direct olefination of the methyl group of toluene derivatives. This reaction provides a straightforward access to allylbenzene derivatives from electron-deficient internal alkynes, although it suffers from low yields when terminal alkynes are used.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588793.

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(22) **Alkyl Arylalkenoates 3a–l; General Procedure**
A sample tube was charged with TBAI (74 mg, 20 mol%), 70% aq TBHP (2.0 mmol), and the appropriate alkyne **2** (1.0 mmol), and the mixture was stirred for 15 min at 25 °C. The appropriate toluene derivative **1** (1.5 mL) was added and the mixture was stirred under vacuum at 80 °C for 14 h. The crude mixture was then concentrated in vacuo, and the reaction was quenched by addition of sat. aq $Na_2S_2O_3$ (3.0 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (8:1)].
Dimethyl 2-Benzylfumarate (**3a**)
Colorless oil; yield: 0.17 g (84%). IR (KBr): 3035, 2928, 1728, 1715, 1311, 1108 cm^{-1}; ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.57 (s, 2 H), 3.78 (s, 3 H), 3.89 (s, 3 H), 6.38 (s, 1 H), 7.23 (d, ^3J = 7.0 Hz, 2 H), 7.28–7.332 (m, 3 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 45.6 (CH_2), 53.3 (OCH_3), 54.7 (OCH_3), 127.7 (CH), 128.7 (2 CH), 129.3 (2 CH), 131.9 (CH), 136.1 (C), 147.7 (C), 165.5 (C=O), 167.0 (C=O). MS: *m/z* (%) = 234 (M^+, 3), 219 (21), 188 (47), 116 (71), 91 (100). Anal. Calcd for $C_{13}H_{14}O_4$ (234.25): C, 66.66; H, 6.02. Found: C, 66.95; H, 6.41.
Dimethyl 2-(4-Chlorobenzyl)fumarate (**3b**)
Colorless oil; yield: 0.23 g (86%). IR (KBr): 3014, 2971, 1735, 1721, 1316, 1135 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.46 (s, 2 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 6.42 (s, 1 H), 7.32 (app d, ^3J = 7.1 Hz, 2 H), 7.45 (app d, ^3J = 7.1 Hz, 2 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 48.6 (CH_2), 53.3 (OCH_3), 54.3 (OCH_3), 128.6 (2 CH), 129.0 (2 CH), 133.8 (CH), 134.0 (C), 135.6 (C), 147.3 (C), 165.4 (C=O), 167.1 (C=O). MS: *m/z* (%) = 268 (M^+, 1), 253 (10), 209 (29), 143 (57), 125 (100), 88 (38). Anal. Calcd for $C_{13}H_{13}ClO_4$ (268.69): C, 58.11; H, 4.88; Cl, 13.19. Found: C, 58.49; H, 5.19; Cl, 13.54.
Dimethyl 2-[(1-Naphthyl)methyl]fumarate (**3h**)
Pale-yellow oil; yield: 0.24 g (86%). IR (KBr): 3043, 2978, 1728, 1716, 1361, 1182 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.89 (s, 3 H), 4.11 (s, 2 H), 6.43 (s, 1 H), 7.06 (d, ^3J = 6.6 Hz, 1 H), 7.25–7.34 (m, 3 H), 7.78 (d, ^3J = 7.0 Hz, 1 H), 7.86 (d, ^3J = 7.1 Hz, 1 H) 7.95 (t, ^3J = 6.7 Hz, 1 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 39.2 (CH_2), 51.4 (OCH_3), 57.4 (OCH_3), 127.7 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 128.9 (C), 129.1 (C), 129.2 (CH), 129.4 (CH), 129.6 (CH), 130.4 (C), 131.1 (CH), 149.2 (C), 165.1 (C=O), 169.4 (C=O). MS: *m/z* (%) = 284 (M^+, 2), 269 (12), 238 (41), 166 (46), 143 (69), 141 (100). Anal. Calcd for $C_{17}H_{16}O_4$ (284.31): C, 71.82; H, 5.67. Found: C, 72.34; H, 5.98.
Dimethyl 1*H*-Indene-2,3-dicarboxylate (**4**)
A mixture of fumarate **3c** (1.0 mmol), Pd_2dba_3 (0.05 mmol), tris(2-furyl)phosphine (0.15 mmol), and Cs_2CO_3 (3.0 mmol) in 1,4-dioxane (3.0 mL) was stirred for 30 min at 25 °C. The reaction vessel was evacuated and back-flushed with N_2 (3×), and the mixture was stirred at 90 °C for 18 h. The mixture was then diluted with EtOAc (5.0 mL), sat. aq NH_4Cl (5.0 mL) was added, and the resulting mixture was stirred for an additional 30 min. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (5:1)] to give a yellow oil; yield: 0.21 g (89%). IR (KBr): 3028, 2957, 1735, 1728, 1371, 1107 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 3.57 (s, 3 H), 3.71 (s, 3 H), 4.11 (s, 2 H), 7.11 (d, ^3J = 6.7 Hz, 1 H), 7.23–7.34 (m, 2 H), 7.57 (d, ^3J = 7.1 Hz, 1 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 46.2 (CH_2), 53.0 (OCH_3), 53.6 (OCH_3), 125.3 (CH), 125.9 (CH), 126.5 (CH), 129.1 (CH), 130.3 (C), 133.5 (C), 142.3 (C), 147.8 (C), 165.5 (C=O), 167.1 (C=O). MS: *m/z* (%) = 232 (M^+, 4), 173 (16), 114 (37), 91 (100), 77 (61). Anal. Calcd for $C_{13}H_{12}O_4$ (232.24): C, 67.23; H, 5.21. Found: C, 67.89; H, 5.76.