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Tandem Diels−Alder/Cross-Coupling Reactions of Generated in Situ Organoindium Reagents in a One-Pot Process

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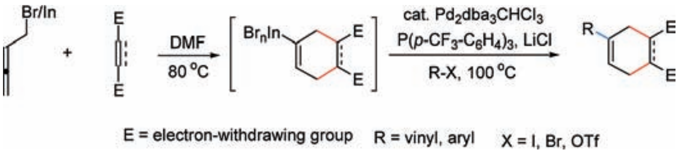
ABSTRACT



Tandem Diels−Alder/ cross-coupling reactions with organoindium reagents generated in situ from 1-bromo-2,3-butadiene and indium were developed in a one-pot process. [4 + 2] Cycloaddition reactions using organoindium reagents and subsequent Pd-catalyzed cross-coupling reactions provided the rapid synthesis of six-membered carbocycles starting from 1-bromo-2,3-butadiene.

Because main group element substituted 1,3-dienes and their synthons play an important role as building blocks in organic synthesis, development of efficient synthetic methods for their preparation has been required. Although a number of 1-main group element substituted 1,3-dienes were reported,[1] 2-main group element substituted 1,3-dienes are rather difficult to prepare and, therefore, rarely reported. In particular, of these compounds, 2-(1,3-butadienyl)magnesium chloride has been known to be a tricky species mainly due to the poor regioselectivity involved during the course of the reactions.[2] While synthesis of 2-phenylseleno- and 2-trialkylstannyl-1,3-butadiene was reported by Bates et al.,[3] 1,3-butadienyl-2-yllithium was indirectly prepared from the 2-stannyl precursor.[4] Preparation of 2-trialkylsilyl-1,3-butadiene and 2-silyl-substituted 1,3-cyclohexadienes was also reported.[5] Eisch and Hoberg reported previously about aluminum-substituted 1,3-dienes.[6] In addition, 1,3-dienyl-2-zirconium compounds were prepared from the reaction of 2-trimethylsilyloxy-1,3-dienes with zirconocene.[7] Recently, Welker et al. reported the preparation of 2-trialkylsiloxy-substituted and 2-KBF$_3$-substituted 1,3-dienes from the treatment of 2-chloro-1,3-butadiene with Mg followed by trimethyl boronate and tri(ethoxysilyl) chloride, respectively.[8]

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(1) (a) Sadykh-Zade, S. I.; Petrov, A. D. *Dokl. Akad. Nauk SSSR* **1957**, *112*, 662. (b) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415. (c) Fleming, I.; Percival, A. *Chem. Commun.* **1976**, 681. (d) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. *Tetrahedron Lett.* **1987**, *28*, 4169. (e) Luh, T. Y.; Wong, K. T. *Synthesis* **1993**, 349. (f) Stadnichuk, M. D.; Voropaeva, T. I. *Russ. Chem. Rev.* **1995**, *64*, 25. (g) Garnier, L.; Plunian, B.; Mortier, J.; Vaultier, M. *Tetrahedron Lett.* **1996**, *37*, 6699.

(2) Nunomoto, S.; Yamashita, Y. *J. Org. Chem.* **1979**, *44*, 4788.

(3) Bates, G. S.; Fryzuk, M. D.; Stone, C. *Can. J. Chem.* **1987**, *65*, 2612.

(4) Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1942.

(5) (a) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, 3323. (b) Daniels, R. G.; Paquette, L. A. *Organometallics* **1982**, *1*, 1449. (c) Ikeda, Z.; Oshima, K.; Matsubara, S. *Org. Lett.* **2005**, *7*, 4859.

(6) (a) Eisch, J. J; Kaska, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 2976. (b) Hoberg, H.; Krausegoing, R. *J. Organomet. Chem.* **1977**, *127*, C29.

(7) Granchegui, B.; Bertus, P.; Szymoniak, J. *Synlett* **2001**, 123.

(8) (a) De, S.; Welker, M. E. *Org. Lett.* **2005**, *7*, 2481. (b) Pidaparthi, R. R.; Welker, M. E.; Day, C. S.; Wright, M. W. *Org. Lett.* **2007**, *9*, 1623. (c) De, S.; Day, C.; Welker, M. E. *Tetrahedron* **2007**, *63*, 10939. (d) Wang, L.; Day, C. S.; Wright, M. W.; Welker, M. E. *Beilstein J. Org. Chem* **2009**, *5*, 45.

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However, synthons for 2-main group element substituted 1,3-dienes such as homoallenyl silane,[9] stannane,[10] and boronate[11] are inconvenient to prepare. Because so much is now known about the Diels−Alder reaction,[12] we were convinced that when we developed an efficient synthon for 2-main group element substituted 1,3-dienes, this would prove useful for the synthesis of six-membered carbocycles bearing a vinyl metal moiety. Recently, we discovered that organoindium reagents generated in situ from the reaction of indium with 1-bromo-2,3-butadiene or 1,3-dibromo-2-butyne acted as efficient synthons for 1,3-dienyl-2-yl species in Pd-catalyzed cross-coupling reactions[13] and addition reactions to imines and aldehydes.[14] During the course of our research program aimed at finding new indium-mediated organic reactions,[15] we envisioned the possibility of extending the tandem reaction by using an easily accessible homoallenyl indium. Herein, we report tandem Diels−Alder/cross-coupling reactions with organoindium reagents generated in situ from 1-bromo-2,3-butadiene and indium in a one-pot process, producing cyclohexene derivatives via formation of 1-cyclohexenyl-1-indium (Scheme 1).

Scheme 1. Tandem Diels−Alder Reaction/Cross-Coupling Reaction

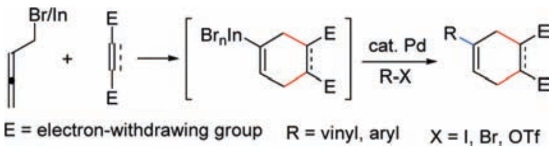
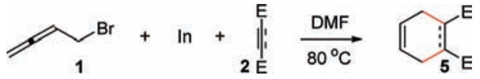
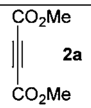
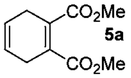
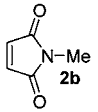
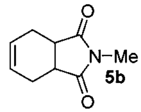
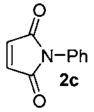
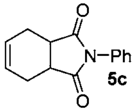
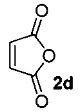
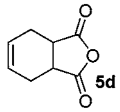
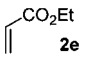
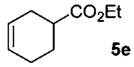
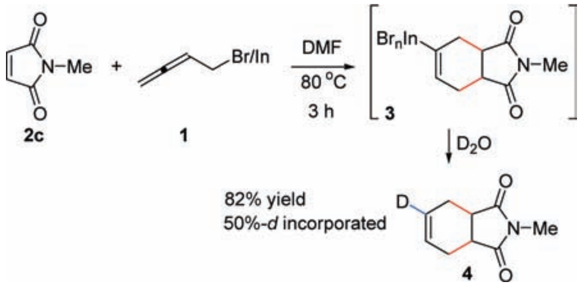


Table 1. Diels−Alder Reaction of Organoindium with Dienophile[a]



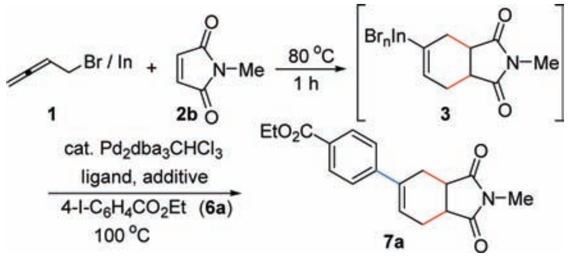
entry	dienophile	adduct	time (h)	yield (%)
1[b]	 **2a**	 **5a**	3	83
2	 **2b**	 **5b**	2	82[c]
3[b]	 **2c**	 **5c**	1	76[c] (16)[d]
4	 **2d**	 **5d**	2	83[c]
5	 **2e**	 **5e**	2	84

[a] **1** (0.75 mmol), In (0.5 mmol), and **2** (0.5 mmol) in DMF (0.25 M) was used. [b] 2 equiv of **2** was used. [c] Cis. [d] **2**.



First, we examined whether organoindium reagents generated in situ from 1-bromo-2,3-butadiene and indium could work as an efficient partner suitable for a Diels−Alder reaction with dienophiles (Table 1). When *N*-methylmaleimide **2b** (0.5 mmol) was treated with organoindium reagent, generated in situ from 1-bromo-2,3-butadiene **1** (0.75 mmol) and indium (0.5 mmol) in DMF, at 80 °C for 2 h, tetrahydroisoindole-1,3-dione **5b** was obtained in 82% yield (entry 2). This result implies that the organoindium reagent acted efficiently as 1,3-butadienyl-2-ylindium. Quenching of the reaction mixture with D_2O after the initial Diels−Alder reaction gave rise to the corresponding deuterated adduct **4** in 82% yield with 50% *d*-incorporation, indicating that 1-cyclohexenyl-1-indium **3** was indeed

Table 2. Optimization of Tandem Diels−Alder/Cross-Coupling Reaction[a]

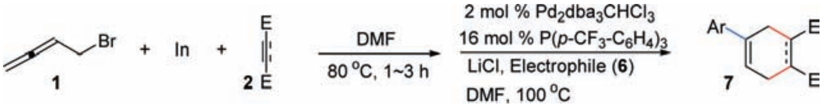


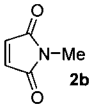
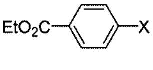
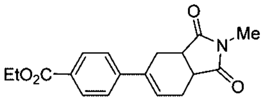
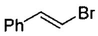
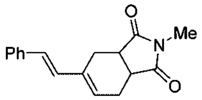
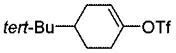
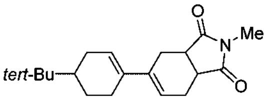
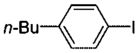
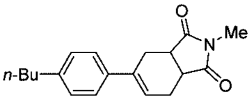
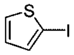
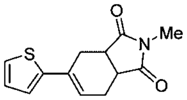
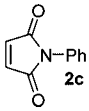
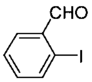
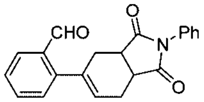
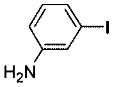
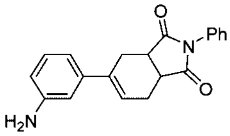
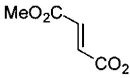
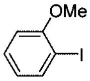
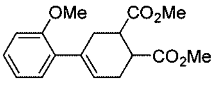
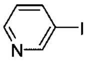
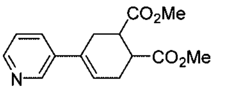
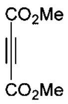
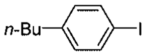
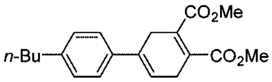
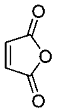
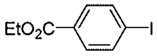
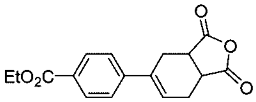
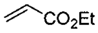
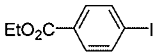
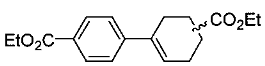
entry	ligand	additive	solvent	time (h)	yield[b] (%)	
					5b	**7a**
1	16 PPh_3	LiI	DMF	2	26[c]	48[c]
2	8 Xantphos	LiI	DMF	3	13	43
3	8 DPEphos	LiI	DMF	3	6	33
4	8 DPPF	LiI	DMF	2	5	47
5	16 P(2-furyl)$_3$	LiI	DMF	2	11	69 (64)[c]
6	16 (biphenyl)Pcy$_2$	LiI	DMF	2	13	31
7	16 $P(C_6F_5)_3$	LiI	DMF	2	5	66 (60)[c]
8	16 P(p-MeO-C_6H_4)$_3$	LiI	DMF	3		26
9	16 P(p-CF_3-C_6H_4)$_3$		DMF	2		52[c]
10	16 P(p-CF_3-C_6H_4)$_3$	LiI	DMF	2		70[c]
11	16 P(p-CF_3-C_6H_4)$_3$	LiI[d]	DMF	2		5
12	16 P(p-CF_3-C_6H_4)$_3$	LiI	THF	2	65	28
13	16 P(p-CF_3-C_6H_4)$_3$	LiI	CH_3CN	3	7	56 (54)[c]
14[e]	16 P(p-CF_3-C_6H_4)$_3$	LiI	DMF	2	8	92 (89)[c]
15[e]	16 P(p-CF_3-C_6H_4)$_3$	LiCl	DMF	2		93[c]
16[e]	16 P(p-CF_3-C_6H_4)$_3$	LiBr	DMF	2		84[c]

[a] 2 mol % of $Pd_2dba_3CHCl_3$, **1** (1.5 equiv), **6a** (1 equiv), In (1 equiv), **2b** (1.5 equiv), and additive (1 equiv) were used. Stereochemistry of **7a** is cis. [b] GC yield based on $C_{14}H_{30}$ as an internal standard. [c] Isolated yield. [d] LiI (2 equiv) was used. [e] **1** (2.3 equiv) was used.

formed. Next, we applied these conditions to a variety of dienophiles. *N*-Phenylmaleimide afforded the corresponding adduct (**5c**) in 76% yield under the optimum reaction conditions (entry 3). DMAD reacted with the organoindium reagent in DMF at 80 °C for 3 h, producing 1,2-bis(methoxycarbonyl)-1,4-cyclohexadiene **5a** in 83% yield (entry 1). We were particularly pleased to obtain cyclohexene adducts in 83% and 84% yields, respectively, from the reaction with maleic anhydride and ethyl acrylate (entries 4 and 5).

Table 3. Tandem Diels−Alder/Cross-Coupling Reaction in a One-Pot Process[a]



entry	dienophile	electrophile	product	time (h)	yield (%)
1	 **2b**	 X = Cl	 **7a**[b]	6	0
2		Br		3	76
3		I		2	93
4		OTf		4	72
5	**2b**		 **7b**[b]	2	81
6	**2b**		 **7c**[b]	2	88 (1:1.3)[c]
7	**2b**		 **7d**[b]	3	72
8	**2b**		 **7e**[b]	2	60
9[d]	 **2c**		 **7f**[b]	3	79
10	**2c**		 **7g**[b]	2	73
11[e]	 **2f**		 **7h**[f]	3	60
12[e]	**2f**		 **7i**[f]	2	78
13[d]	 **2a**		 **7j**	2	68
14	 **2d**		 **7k**[b]	2	53
15	 **2e**		 **7l**	2	86(1:4)[g]

[a] Reaction were carried out with **1** (1.1 mmol), In (0.75 mmol), and **6** (0.5 mmol) in DMF (0.25 M). [b] Cis. [c] Diastereomeric ratio. [d] **2** (3 equiv) was used. [e] Reactions were carried out with **1** (1.5 mmol), In (1.0 mmol), In (1.0 mmol), **2** (1.0 mmol), and **6** (0.5 mmol). [f] Trans. [g] Ratio of *meta*- and *para*-isomers.

Next, detection of cyclohexenylindium as an intermediate led us to investigate tandem Diels−Alder/ cross-coupling reactions using 1-bromo-2,3-butadiene and indium in a one-pot process. These results are summarized in Table 2. After *N*-methylmaleimide **2b** reacted with organoindium reagents in DMF, the reaction mixture was treated with ethyl 4-iodobenzoate in the presence of a variety of Pd catalysts to provoke tandem Diels−Alder/cross-coupling reactions. Of the catalytic systems examined, the best results were obtained with 2 mol % of $Pd_2dba_3CHCl_3$ and 16 mol % of $(p\text{-}CF_3\text{-}C_6H_4)_3P$ in the presence of 1 equiv of LiCl in DMF at 100 °C for 2 h under a nitrogen atmosphere, affording **7a** selectively in 93% yield (entry 15). When Ph_3P, Xantphos, or $(biphenyl)PCy_2$ was used, the cross-coupling reactions did not completely proceed (entries 1, 2, and 6). The use of $(p\text{-}MeO\text{-}C_6H_4)_3P$ provided tandem reaction product in only 26% yield (entry 8). THF gave the desired product **7a** in 28% yield together with Diels−Alder adduct **5b** in 65% yield (entry 12). Of the additives examined, LiCl (1 equiv) gave the best results.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of dienophiles and electrophilic coupling partners in the tandem Diels−Alder/cross-coupling reactions. These results are summarized in Table 3. Although ethyl 4-chlorobenzoate did not react with cyclohexenylindium derived from *N*-methylmaleimide, 1-bromo-2,3-butadiene, and indium under the optimum reaction conditions (entry1), the corresponding bromide and triflate produced the desired tandem reaction products **7a** in 76% and 72% yields, respectively (entries 2 and 4). Exposure of cyclohexenylindium to vinyl bromide and vinyl triflate afforded **7b** and **7c** in 81% and 88% (dr = 1:1.3) yields, respectively (entries 5 and 6). The present method worked equally well with diverse aryl iodides such as 4-iodo-*n*-butylbenzene and 2-iodothiophene (entries 7 and 8). Cyclohexenylindium generated in situ from *N*-phenylmaleimide reacted efficiently with 2-iodobenzaldehyde and 3-iodoaniline, producing tandem Diels−Alder/cross-coupling products (**7f** and **7g**) possessing a 2-formylphenyl and a 3-aminophenyl group in 79% and 73% yields (entries 9 and 10). Vinylindium generated in situ from dimethyl fumarate coupled with 2-iodoanisole, affording tandem reaction products (**7h**) in 60% yield (entry 11). 3-Iodopyridine turned out to be compatible with the present reaction conditions, producing adduct **7i** in 78% yield (entry 12). Treatment of cyclohexenylindium generated in situ from DMAD and maleic anhydride with 4-iodo-*n*-butylbenzene and ethyl 4-iodobenzoate provided **7j** and **7k** in 68% and 53% yields, respectively, in a one-pot process (entries 13 and 14). We were pleased to obtain the functionalized cyclohexene **7l** in 86% yield from the reaction of ethyl acrylate with ethyl 4-iodobenzoate (entry 15).

In summary, we have developed an efficient new tandem procedure of Diels−Alder/cross-coupling reactions with organoindium reagents generated in situ from 1-bromo-2,3-butadiene and indium in a one-pot process. [4 + 2] Cycloaddition reactions of organoindium reagents with various dienophiles and subsequent Pd-catalyzed cross-coupling reactions provided the rapid synthesis of six-membered carbocycles starting from aryl bromides and iodides, vinyl bromides and triflates, 1-bromo-2,3-butadiene, and dienophiles.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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