JOC Article

Diversity Synthesis Using the Complimentary Reactivity of Rhodium(II)- and Palladium(II)-Catalyzed Reactions

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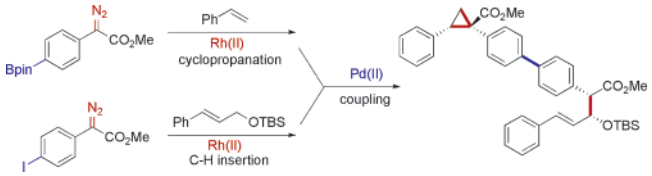
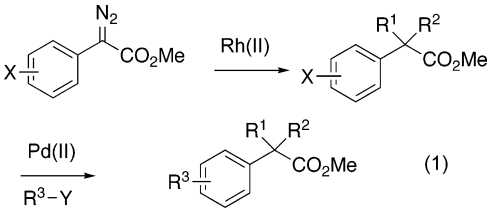


Rhodium(II)-catalyzed reactions of aryldiazoacetates can be conducted in the presence of iodide, triflate, organoboron, and organostannane functionality, resulting in the formation of a variety of cyclopropanes or C−H insertion products with high stereoselectivity. The combination of the rhodium(II)-catalyzed reaction with a subsequent palladium(II)-catalyzed Suzuki coupling offers a novel strategy for diversity synthesis.

Introduction

Metal-catalyzed cross-coupling reactions have become broadly applied in organic synthesis. Several important named reactions such as the Suzuki,[1] Stille,[2] Negishi,[3] and Sonagashira[4] reactions have been developed using this chemistry. The general process relies on the oxidative addition of an organohalide or triflate to a low-valent metal, followed by a metal−halogen (or triflate) exchange with an organometallic species and then a reductive elimination to complete the catalytic cycle. Organohalides and triflates are the most common substrates for the initial oxidative addition, and the reagents for the metal−halogen exchange are typically Grignard, organozinc, organostannane, and organoboron reagents. Palladium and nickel complexes are the best catalysts for this chemistry, although a wide variety of other metals will undergo oxidative addition with organohalides and triflates. Rhodium(I) complexes are very effective catalysts in a variety of reactions involving organohalides and/or organometallics, such as reductive coupling,[5] arylation,[6] and Heck-type reaction/conjugation addition.[7] In contrast, dimeric rhodium(II) complexes do not react with the common functionality used in these coupling reactions, although they are exceptional catalysts for the decomposition of diazo compounds.[8] In this paper we describe the application of the different but complimentary reactivity of the rhodium(II)- and the palladium(II)-catalyzed processes to a two-step sequence applicable to diversity synthesis (eq 1).



(1)

The development of transition-metal-induced cascade and tandem reactions is of intense current interest.[9] Recently, we described a two-step sequence that combined ruthenium-catalyzed enyne metathesis with rhodium-catalyzed tandem cyclopropanation/Cope rearrangement into a rapid method for

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(2) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Espinet, P.; Echavarren, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
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(5) Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193.
(6) (a) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.
(7) (a) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043. (b) Herran, G.; Murcia, C.; Csaky, A. G. *Org. Lett.* **2005**, *7*, 5629.
(8) (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (b) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 47. (c) Padwa, A. *J. Organomet. Chem.* **2005**, *690*, 5533.

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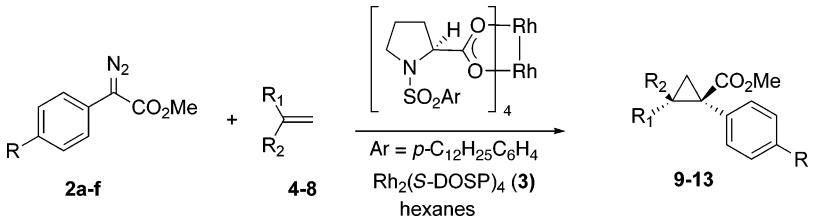
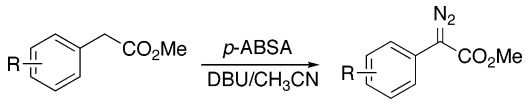
TABLE 1. Enantioselective Cyclopropanation by Aryldiazoacetates[a]



alkene	R_1	R_2	diazo	R	product	yield, %	ee, %	de, %
4	Ph	H	**2a**	*p*-I	**9a**	84	97	>94
4	Ph	H	**2b**	*p*-Bpin	**9b**	80	90	>94
4	Ph	H	**2c**	*p*-$SnBu_3$	**9c**	84	94	>94
4	Ph	H	**2d**	*p*-OTf	**9d**	92	97	>94
4	Ph	H	**2e**	*o*-OTf	**9e**	64	92	>94
4	Ph	H	**2f**	*m*-OTf	**9f**	76	90	90
5	(*p*-Br)Ph	H	**2a**	*p*-I	**10a**	83	92	>94
5	(*p*-Br)Ph	H	**2b**	*p*-Bpin	**10b**	59	91	>94
5	(*p*-Br)Ph	H	**2d**	*p*-OTf	**10d**	73	96	>94
6	(*E*)-PhCH=CH	H	**2a**	*p*-I	**11a**	84	91	>94
6	(*E*)-PhCH=CH	H	**2b**	*p*-Bpin	**11b**	80	89	>94
6	(*E*)-PhCH=CH	H	**2d**	*p*-OTf	**11d**	90	94	>94
7	BuO	H	**2a**	*p*-I	**12a**	79	82	>94
7	BuO	H	**2b**	*p*-Bpin	**12b**	69	70	>94
7	BuO	H	**2d**	*p*-OTf	**12d**	81	87	>94
8	Ph	Ph	**2a**	*p*-I	**13a**	86	99	-
8	Ph	Ph	**2b**	*p*-Bpin	**13b**	84	98	-
8	Ph	Ph	**2d**	*p*-OTf	**13d**	80	99	-

[a] 2.5 mmol substrate, 0.5 mmol diazo compound, 1% Rh_2(*S*-DOSP)$_4$, 1 h addition, −40 °C to rt, hexanes.

SCHEME 1



Compound	R	yield, %
a	*p*-I	89
b	*p*-Bpin	81
c	*p*-$SnBu_3$	66
d	*p*-OTf	73
e	*o*-OTf	73
f	*m*-OTf	83

the construction of highly functionalized cycloheptane derivatives.[10] Another useful combination would be the stereoselective reactions of donor-/acceptor-substituted carbenoids followed by palladium-catalyzed coupling reactions. Examples exist that demonstrate the compatibility of rhodium(II)-catalyzed carbenoid chemistry with the functionality commonly used in the cross-coupling chemistry. Effective intramolecular C−H insertion can occur in a substrate containing an aryl triflate.[11] Allylstannanes undergo intermolecular cyclopropanation with vinyldiazoacetates.[12] An *o*-iodophenyl diazoamide is capable of a rhodium(II)-catalyzed cyclization without interference by the iodine group.[13] If the carbenoid chemistry was followed by a cross-coupling reaction, the sequence would be a useful strategy for diversity synthesis.

Results and Discussion

The standard method for the synthesis of aryldiazoacetates has been to use a diazotransfer reaction with *p*-(acetamido)-benzenesulfonyl azide (*p*-ABSA) in the presence of DBU as base.[14] A similar reaction with the derivatized aryl acetates **1** proceeded uneventfully to form the aryldiazoacetates **2** in good yield (Scheme 1). The iodide (**2a**), organoboron (**2b**), organostannane (**2c**), and triflate (**2d**−**f**) groups were fully compatible with the diazo-transfer reaction.

To evaluate the influence of the various groups on the outcome of rhodium(II)-catalyzed carbenoid chemistry, a series of cyclopropanation reactions were conducted using the aryldiazoacetates **2**. The dirhodium tetraprolinate, Rh_2(*S*-DOSP)$_4$ (**3**), has been shown to be an exceptional chiral catalyst for the reactions of simple aryldiazoacetates[15] and was used as the standard catalyst in this study. The optimum temperature for the highest yields and enantioselectivity was −40 °C followed by gradual warming to room temperature. All six of the aryldiazoacetates **2a**−**f** reacted with styrene,[16] and, in each case, the cyclopropanes **9a**−**f** were produced in good yields (64−92%), diastereoselectivity (90−94% de), and enantioselectivity (90−97% ee). The iodide (**2a**), organoboron (**2b**), and triflate

(9) (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (b) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694. (c) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (d) Padwa, A.; Zhang, Z. J.; Zhi, L. *J. Org. Chem.* **2000**, *65*, 5223. (e) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326. (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289.

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(12) Lin, Y.; Turos, E. *J. Organomet. Chem.* **2001**, *630*, 57.

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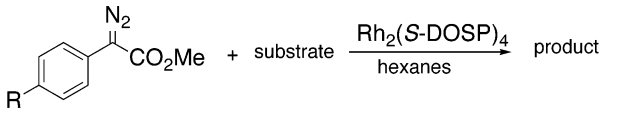
(14) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

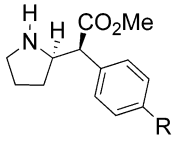
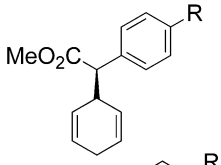
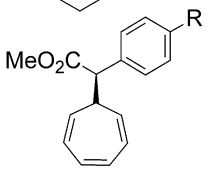
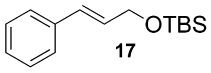
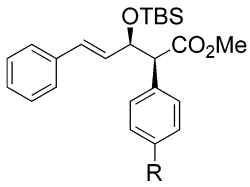
(15) For recent reviews: (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Loe, Ø. *Synthesis* **2004**, *16*, 2595.

(16) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

TABLE 2. C−H Insertions with Aryldiazoacetates[a]



2a,b,d **14-17** **18-21a,b,d**

substrate	diazo	R	product	yield, %	ee, %	de, %
 **14**	**2a**	*p*-I	 **18a**	41	70	>94
	2b	*p*-Bpin	**18b**	0	–	>94
	2d	*p*-OTf	**18d**	48[a]	85	>94
 **15**	**2a**	*p*-I	 **19a**	74	95	–
	2b	*p*-Bpin	**19b**	62	89	–
	2d	*p*-OTf	**19d**	59	94	–
 **16**	**2a**	*p*-I	 **20a**	58	91	–
	2b	*p*-Bpin	**20b**	58	88	–
	2d	*p*-OTf	**20d**	52	95	–
 **17**	**2a**	*p*-I	 **21a**	95[b]	84	>94
	2b	*p*-Bpin	**21b**	74[b]	89	>94
	2d	*p*-OTf	**21d**	59[c]	74	>94

[a] 2.5 mmol substrate, 0.5 mmol diazo compound, 1% Rh_2(*S*-DOSP)$_4$, 1 h addition, −40 °C to rt, hexanes. a: same conditions but at 25 °C. b: 0.5 mmol substrate, 1 mmol diazo, 1% Rh_2(*S*-DOSP)$_4$, 1 h addition, −40 °C to rt. c: 0.5 mmol substrate, 1 mmol diazo, 2% Rh_2(*S*-DOSP)$_4$, 2 h addition, 50 °C.

(**2d**) aryldiazoacetates were then tested with a variety of other electron-rich alkenes,[17] and, in all cases, highly stereoselective and high-yielding reactions were obtained. The absolute configuration of the products was assigned by analogy to the results obtained with simpler aryldiazoacetates.[15−17] These results demonstrate that the iodide, organoboron, organostannane, and triflate groups do not interfere with the cyclopropanation chemistry of aryldiazoacetates.

A more demanding reaction for aryldiazoacetates is intermolecular C−H activation by means of carbenoid-induced C−H insertion.[15] This has great potential for application in diversity synthesis, but the substrates are less reactive toward the carbenoids than the electron-rich alkenes used in Table 1.[14] The functionalized aryldiazoacetates **2** were reacted with representative substrates capable of intermolecular C−H activation (Table 2). In most cases, the C−H activation products were formed, but the yields and stereoselectivity were not always as high as the reactions with the simpler aryldiazoacetates. The reaction of *N*-Boc-pyrrolidine (**14**)[18] with the triflate derivative **2d** was not efficient at −40 °C, but reasonable yield and enantioselectivity were observed in reactions conducted at room temperature. The enantioselectivity in the reaction of *N*-Boc-pyrrolidine **14** with the iodo derivative **2a** was only 70% ee, but the diastereoselectivity remained high. No product was obtained in the reaction of *N*-Boc-pyrrolidine **14** with the organoborane **2b**. For all these reactions the yield and enantioselectivity were determined from the products after removal of the Boc group. The reactions of the aryldiazoacetates **2a**, **2b**, and **2d** with 1,4-cyclohexadiene **15**,[19] cycloheptatriene **16**,[20] and the allyl silyl ether **17**[21] proceeded in good yields and stereoselectivity except for the reaction of the triflate **2d** with **17**, in which a reasonable yield of **21d** could only be obtained by running the reaction with **2d** as the limiting agent at elevated temperature. The absolute configuration of the products was assigned by analogy to the results obtained with simpler aryldiazoacetates.[18−21] These results indicate that enantioselective intermolecular C−H activation can be achieved in the presence of the cross-coupling functionality, but reactive substrates are required and the yields and the steroselectivity do not always match the results obtained with the simpler aryldiazoacetates.

Having developed a practical method for the synthesis of various triflate derivatives, the next stage was to apply these substrates in cross-coupling reactions. Even though a number of highly effective methods have been recently developed for

(17) (a) Davies, H. M. L.; Nagashima, T.; Klino, J. L. *Org. Lett.* **2000**, *2*, 823. (b) Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *Chem. Commun.* **1998**, 2377.

(18) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462.

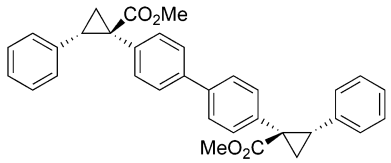
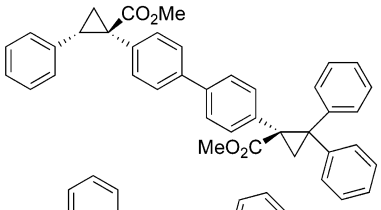
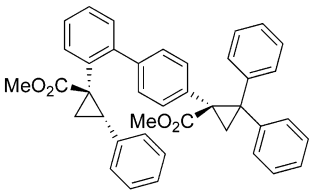
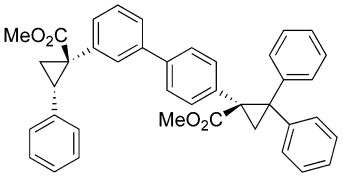
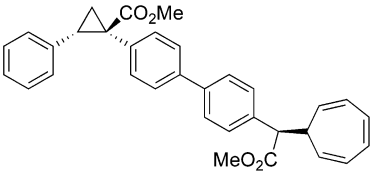
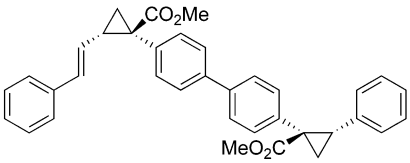
(19) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

(20) Davies, H. M. L.; Stafford, D. G.; Hansen, T.; Churchill, M. R.; Keil, K. M. *Tetrahedron Lett.* **2000**, *41*, 2035.

(21) Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126.

TABLE 3. Cross-coupling of Aryl Triflates with Arylboronates[a]

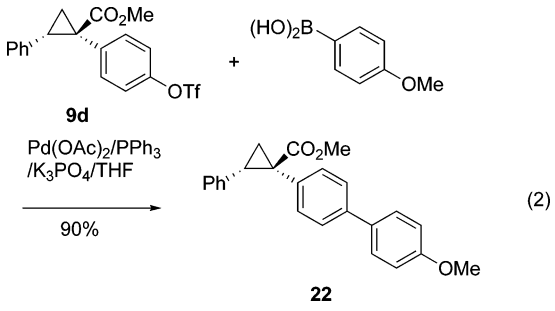
ArOTf + Ar-Bpin —$Pd(OAc)_2$ (10 mol%), K_3PO_4/THF reflux 20h→ Product

ArOTf	Ar-Bpin	product		yield, %
9d	**9b**		**23**	68
9d	**13b**		**24**	83
9e	**13b**			0
9f	**13b**		**25**	92
9d	**20b**		**26**	57
11d	**9b**		**27**	74

[a] Standard conditions: Ar−Bpin, 1.0 equiv; reaction time, 20 h; $Pd(OAc)_2$, 10 mol %; PPh_3, 40 mol %; K_3PO_4, 3 equiv; THF. All substrates were recrystallized to >97% ee.

palladium-catalyzed cross-coupling reactions,[22] we found that the older standard reaction conditions ($Pd(OAc)_2/PPh_3/K_3PO_4$) worked very well with these substrates, as illustrated in the coupling of the cyclopropyl triflate **9d** with *p*-methoxyphenylboronate to form the biaryl **22** in 90% yield (eq 2).

The rhodium(II)-catalyzed carbenoid chemistry is capable of generating both of the coupling partners required for the palladium-catalyzed cross-coupling reactions. Particularly advantageous is the fact that the carbenoid reactions proceed with very high enantioinduction, and, in many instances, a single

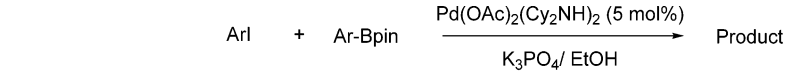


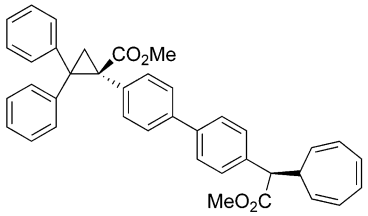
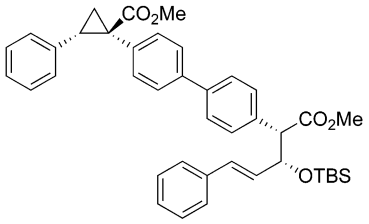
(2)

recrystallization generates material that is essentially a single enantiomer. The palladium acetate-catalyzed coupling of various aryl triflates with the pinacolboron derivatives is illustrated in Table 3. The *para*- and *meta*-substituted triflates, **9d** and **9f** gave

(22) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (c) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

TABLE 4. Cross-coupling of Aryl Iodides with Arylboronates[a]



ArI	Ar-Bpin	product		yield, %
13a	**20b**		**28**	79
21a	**9b**		**29**	66

[a] Coupling conditions: Ar−Bpin, 1.0 equiv; $Pd(OAc)_2(Cy_2NH)_2$, 5 mol %; K_3PO_4, 3 equiv; EtOH; 16 h.

high-yielding reactions but the *ortho*-substituted triflate **9e** failed to give any cross-coupling product under these reaction conditions.

The cross-coupling reactions were also conducted between aryl iodides and aryl pinacolboronates. Two examples of cross-coupling reactions between cyclopropanes and C−H insertion products are shown in Table 4. The recently published procedure using preformed DAPCy (*trans*-$(Cy_2NH)_2Pd(OAc)_2$) as the catalyst gave effective coupling at room temperature.[23]

In conclusion, this study demonstrates the complimentary nature of rhodium(II)- and palladium(II)-catalyzed reactions for diversity synthesis. Aryldiazoacetates containing reactive functionality for palladium-catalyzed cross-coupling reactions are capable of effective rhodium(II)-catalyzed carbenoid chemistry without interference from the additional functionality. A subsequent palladium-catalyzed cross-coupling reaction has the potential to generate a diverse range of products.

Experimental Section

Typical Procedure for Rhodium-Catalyzed Reactions. (1*R*,2*S*)-Methyl 1-(4-iodophenyl)-2-phenylcyclopropanecarboxylate (**9a**): A solution of **2a** (151 mg, 0.5 mmol) in hexanes (10 mL) was added over 1 h using a syringe pump to a solution of Rh_2(*S*-DOSP)$_4$ (9.4 mg, 1 mol %) and styrene (260 mg, 2.5 mmol) in hexanes (5 mL) at −40 °C. After the addition was complete, the reaction was warmed to 23 °C and stirred for 1 h. The solvent was removed under reduced pressure, and the diastereoselectivity was determined to be >94% de by ^{1}H NMR analysis of the crude reaction mixture. The residue was purified by flash chromatography (Et_2O/pentane = 1/20) to give the title compound **9a** (160 mg, 84% yield) as a colorless oil. $[\alpha]_D^{25}$ +9 (*c* = 1.0, $CHCl_3$); 97% ee (*R*,*R*-Whelk column, 2% *i*-PrOH in hexanes, 1.0 mL/min, λ = 254 nm, t_R = 9.4, minor; 11.4, major); IR (neat): 3033, 2951, 2852, 1720, 1490, 1435, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 2H), 7.10−7.08 (m, 3H), 6.78−6.75 (m, 4H), 3.66 (s, 3H), 3.10 (dd, J = 9.0, 7.5 Hz, 1H), 2.13 (dd, J = 9.0, 5.0 Hz, 1H), 1.83 (dd, J = 7.5, 5.0 Hz, 1H); ^{13}C NMR DEPT (75 MHz, $CDCl_3$) δ 173.6 (C), 136.8 (CH), 135.8 (C), 134.6 (C), 133.8 (CH), 127.9 (CH), 127.8 (CH), 126.5 (CH), 92.9 (C), 52.6 (CH_3), 36.8 (C), 33.0 (CH), 20.2 (CH_2); LRMS (ESI) *m*/*z* (rel intens) 378 (100). HRMS (EI). Calcd for $C_{17}H_{15}IO_2$ (M^+): 378.0111. Found: 378.0118. Anal. Calcd for $C_{17}H_{15}IO_2$: C, 53.99; H, 4.00. Found: C, 54.21; H, 4.14.

Detailed procedures for all new products formed in this paper are available as Supporting Information.

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

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