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A NOVEL INDOLE SYNTHESIS *VIA* CONJUGATE ADDITION OF PYRROLIDINE TO *O*-NITROPHENYLACETYLENES†

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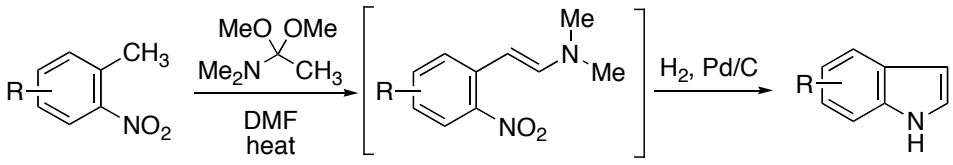
Abstract – A novel indole synthesis reaction by conjugate addition of pyrrolidine to *o*-nitrophenylacetylenes and subsequent reductive cyclization of *o*-nitroarylenamines was developed.

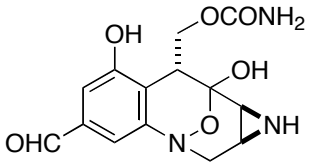
The indole skeleton is commonly found in many natural products, and many of them possess significant biological activities. Therefore, the development of methodologies for indole synthesis has long been a subject of active research in synthetic organic chemistry.[1] While a number of methods have already been well established, there appear to be few practical procedures available. Among them, the Leimgruber-Batcho indole synthesis, involving the formation of *o*-nitrophenyl enamines by heating a mixture of *o*-nitrotoluenes and dimethylformamide dimethyl acetal and subsequent reductive cyclization (Scheme 1), has enjoyed widespread use from laboratory to industry owing to the demonstrated generality and the high functional group compatibility.[2,3] While this protocol is particularly useful for the synthesis of indoles having substituents on the carbocyclic ring, it is difficult to apply this procedure to the direct construction of indoles bearing substituents at the 2- and/or 3-positions.[4]



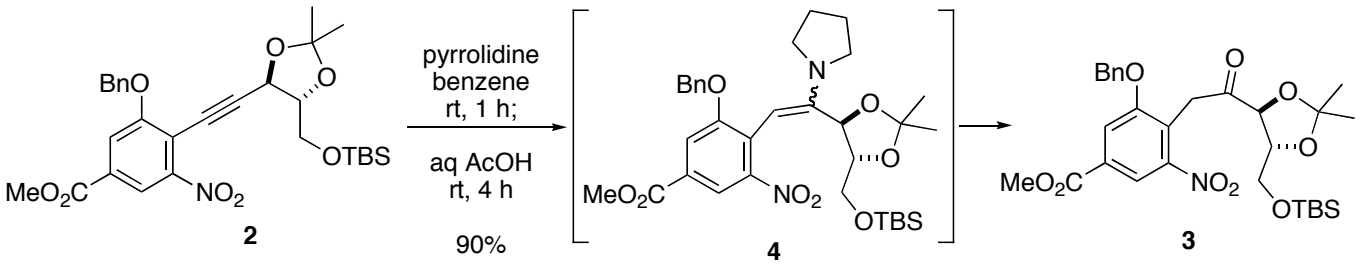
Scheme 1 Leimgruber-Batcho indole synthesis.

†This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

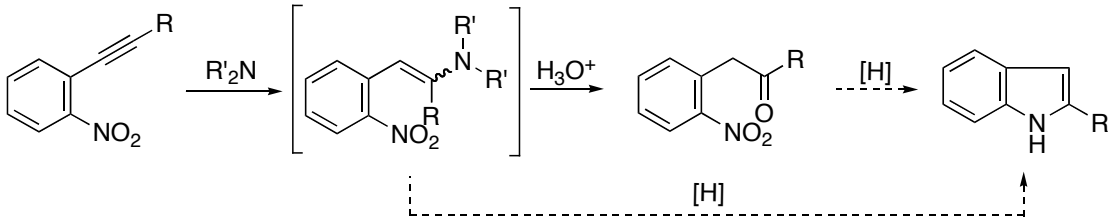
In the course of our synthetic studies on the antitumor antibiotic FR900482 (**1**), we have established a unique transformation of *o*-nitroarylacetylene (**2**) to the corresponding ketone (**3**) (Scheme 2).[5] The unprecedented regioselective addition of pyrrolidine to *o*-nitroarylacetylene[6] (**2**) gave exclusively the enamine **4**, which was converted to ketone (**3**) upon acidic hydrolysis. Considering the formation of enamine intermediate in the Leimgruber-Batcho protocol (Scheme 1), we envisioned that reduction of the nitro group of the resultant enamines would promote cyclization to give 2-substituted indoles (Scheme 3). With this idea in mind, we investigated the generality of this conjugate addition reaction and its application to indole synthesis. Herein we report a novel and efficient synthesis of 2-substituted indoles *via* the conjugate addition of secondary amines to *o*-nitrophenylacetylenes followed by reductive cyclization.



FR-900482 (**1**)



Scheme 2 A key transformation in the total synthesis of FR-900482 (**1**).

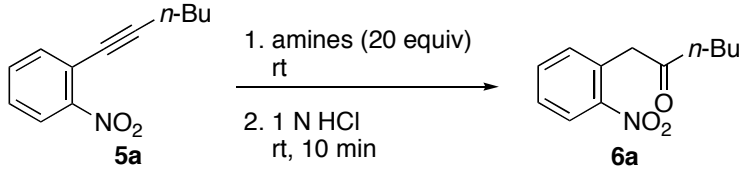


Scheme 3 Proposed indole synthesis *via* conjugate addition to *o*-nitroarylacetylene.

Our initial investigation using *o*-(1-hexynyl)nitrobenzenes (**5a**) revealed that the reaction rate of the conjugate addition is highly dependent both on the structure of the amines and on the electron density of the benzene ring. Cyclic secondary amines such as pyrrolidine, piperidine, and morphorine smoothly added to the substrate **5a** at room temperature (Table 1, entries 1-3). In all cases, good to excellent yields of the corresponding ketone **6a** was obtained after removal of excess amines under reduced pressure and acidic hydrolysis. In contrast, acyclic secondary amines and primary amines showed poor reactivity, and a substantial amount of the starting compound **5a** was recovered even after a day of reaction. The reaction was also highly affected by substituents on the aromatic ring (Table 2). In the case of the

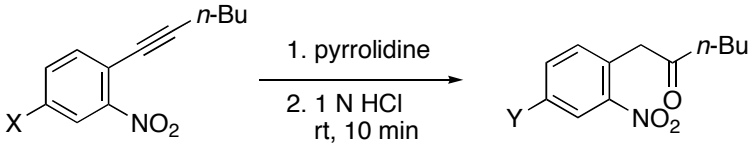
2,4-dinitrophenylacetylene derivative **5b**, the desired reaction took place rapidly at room temperature, even with a reduced amount (5 equiv) of pyrrolidine (entry 1). On the other hand, 2-nitro- and 4-methoxy-2-nitrophenylacetylene derivatives (**5a** and **5c**) were less reactive, and it took from 10 to 36 hours to complete the reaction at 50 °C in acetonitrile. The reaction time could be shortened to several hours by heating with excess (ca. 20 equivs) pyrrolidine without solvent at 80 °C.

Table 1 Conjugate addition of various amines to *o*-nitrophenyacetylene.



Entry	Amines	Time (h)	**6a** (%Yield)	Recovery of **5a** (%)
1	pyrrolidine	2	95	–
2	piperidine	8.5	83	–
3	morphorine	24	90	6
4	diethylamine	24	18	69
5	benzylamine	24	37	56

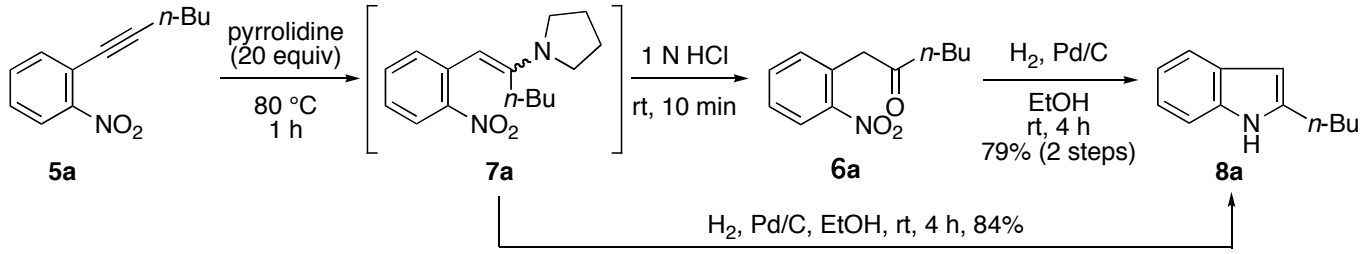
Table 2. Conjugate addition of pyrrolidine to *o*-nitrophenylacetylene.



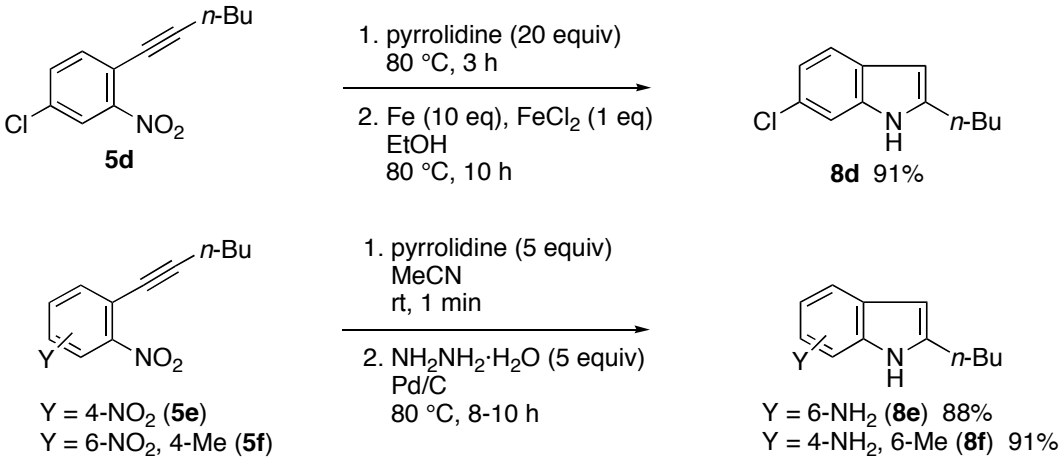
Entry	X	Pyrrolidine (equiv)	Solvent	Temp (°C)	Time (h)	%Yield
1	NO_2 (**5b**)	5	MeCN	rt	1/60	88 (**6b**)
2	H (**5a**)	5	MeCN	50	10	99 (**6a**)
3	H (**5a**)	20	none	80	1	96 (**6a**)
4	MeO (**5c**)	5	MeCN	50	36	87 (**6c**)
5	MeO (**5c**)	20	none	80	3	85 (**6c**)

We then examined the indole formation reaction by reductive cyclization (Scheme 4). Upon hydrogenation of the ketone **6a** over Pd on carbon, the expected indole formation took place smoothly to give 2-*n*-butylindole **8a** in 79% yield (2 steps from **5a**). More conveniently, the indole formation was carried out by reduction of the crude enamine product **7a**.[7] For substrates bearing substituents susceptible to hydrogenation over Pd on carbon, alternative reductive conditions were examined. For example, reductive dechlorination observed in the case of **5d** was completely suppressed by the use of a combination of Fe and $FeCl_2$ (Scheme 5), leading to the desired 2-butyl-7-chloroindole (**8d**) in 91% yield. Reactions of dinitrophenylacetylene derivatives (**5e** and **5f**) provided a complex mixture of byproducts either by hydrogenation over Pd on carbon or by reduction with a combination of Fe and $FeCl_2$. After

survey of the reduction conditions, we have found that reaction with Pd on carbon in the presence of 5 equivalents of hydrazine gives the corresponding amino indoles (**8e** and **8f**) in high yields (Scheme 5).[8]



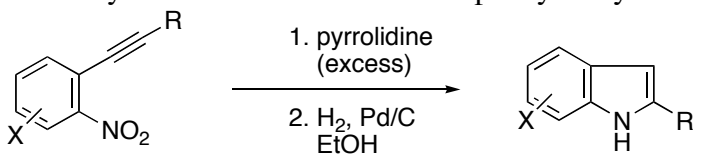
Scheme 4 Indole formation by reductive cyclization.

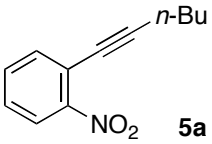
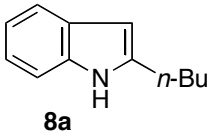
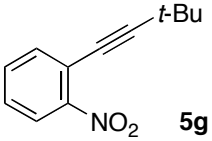
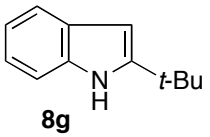
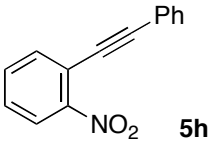
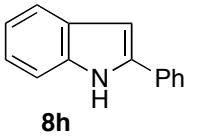
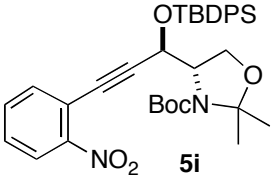
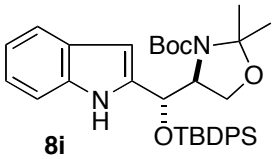
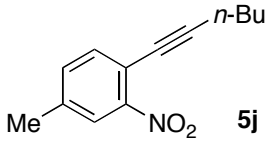
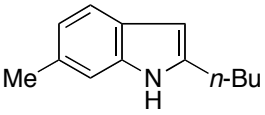
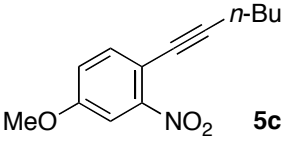
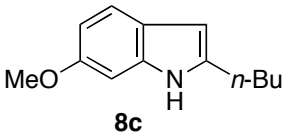
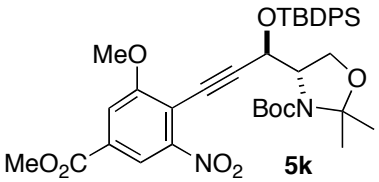
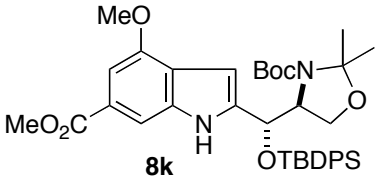


Scheme 5 Reaction of substrates bearing chloro and nitro groups.

The generality of the conjugate addition-reductive indole formation sequence was studied using a variety of substrates which were prepared by Sonogashira-coupling[9] between *o*-nitrophenol triflates and terminal acetylenes (Table 3). The sequential reactions of substrates bearing *n*-butyl, *tert*-butyl, and phenyl groups at the terminus of the arylacetylenes gave the corresponding 2-substituted indoles in good to excellent yields (entries 1-3). The protocol was found to be amenable to the synthesis of indole derivatives **8i** having the fully protected aminodiol substituent derived from (*S*)-serinal, demonstrating the compatibility of siloxy, carbamate, and acetonide groups with the reaction conditions (entry 4). This protocol is also effective for the synthesis of indoles bearing substituents on the carbocyclic ring. Thus, in addition to chloro and amino substituents (Scheme 5), methyl, methoxy, and methoxycarbonyl groups could be accommmodated on the carbocyclic ring of the indoles. One of the drawbacks of this process is that the reductive cyclization step of substrates bearing sterically hindered groups at the acetylene terminus is considerably slower and overall yields are relatively low (entry 4 and 7). We have also found that the yield of the reaction of this type of substrate was improved by a stepwise protocol *via* conversion of the enamine intermediate to the corresponding ketone by acidic treatment, followed by reductive cyclization with a combination of Fe and $FeCl_3$, leading to the highly substituted indoles in good yield (Scheme 6).

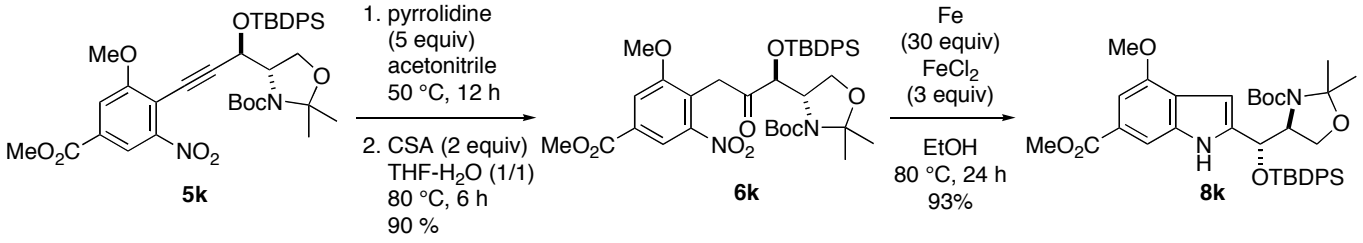
Table 3 Indole synthesis with various *o*-nitrophenylacetylenes.



Entry	Substrate	Conjugate Addition Temp (°C)	Conjugate Addition Time (h)	Reduction Temp (°C)	Reduction Time (h)	Product	%Yield
1	 **5a**	80	1	rt	4	 **8a**	84
2	 **5g**	80	2	rt	1	 **8g**	91
3	 **5h**	80	1	60	10	 **8h**	99
4	 **5i**	50	10	60	48	 **8i**	60
5	 **5j**	80	3	60	10	 **8j**	97
6	 **5c**	80	3	60	12	 **8c**	90
7[a]	 **5k**	50	12	60	48	 **8k**	60

[a]Pyrrolidine (5 equiv) in acetonitrile was used.

In summary, we have developed a novel synthesis of 2-substitituted indoles *via* enamine formation by conjugate addition of pyrrolidine to *o*-nitrophenylacetylene derivatives and subsequent reductive cyclization. The reaction sequence can easily be conducted on a large scale and proceeds under relatively mild conditions, which a variety of functionalities including both acid and base labile groups can tolerate.



Scheme 6 Stepwise protocol *via* conversion of enamine to ketone.

This is advantageous over the other representative 2-substituted indole synthesis from phenylacetylene derivatives, such as 5-*exo-dig* type cyclizations of *o*-alkenylanilines,[10] which require strong basic conditions[11] or heating conditions in the presence of stoichiometric amounts of Cu(I)[12] or the relatively valuable Pd(II) catalysts.[13] Thus, this protocol would effectively serve as a mild and practical method to form 2-subsituted indoles from *o*-nitrophenylacetylene derivatives.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. For recent representative reviews, see: (a) J. A. Joule, 'Indole and Its Derivatives, in Science of Synthesis: Houben-Weyl Methods of Molecular Transformations,' Category 2, Vol. 10, Chapter 10.13, ed. by E. J. Thomas, Georg Thieme Verlag, Stuttgart, 2000. (b) R. J. Sundberg, 'Indoles, Best Synthetic Methods,' ed. by A. R. Katritzky, E. Meth-Cohn, and C. W. Rees, Academic Press, London, 1996. (c) 'Comprehensive Heterocyclic Chemistry II,' ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Vol. 2, Chapters 2.01-2.04, 'Pyrroles and their Benzo Derivatives' Pergamon, Elsevier Science Ltd., Oxford, 1996. (d) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045. (e) G. Battistuzzi, S. Cacchi, and G. Fabrizi, *Eur. J. Org. Chem.,* 2002, 2671. (f) H. Tokuyama and T. Fukuyama, *Chem. Rec.*, 2002, **2**, 37. (g) Y. Kobayashi and T. Fukuyama, *J. Heterocycl. Chem.*, 1998, **35**, 1043.
2. For a review, see: R. D. Clark and D. B. Repke, *Heterocycles*, 1984, **22**, 195.
3. A. D. Batcho and W. Leimgruber, *Org. Synth., Coll. Vol. VII*, 1990, 34.
4. A modification of the Leimgruber-Batcho protocol to synthesize 2- or 3-substituted indoles, see: (a) E. E. Garcia and R. I. Fryer, *J. Heterocycl. Chem.*, 1974, **11**, 219. (b) U. Hengartner, A. D. Batcho, J. F. Blount, W. Leimgruber, M. E. Barscheid, and J. W. Scott, *J. Chem. Soc., Chem. Commun.,* 1987, 1176. (c) W. Haefliger and H. Knecht, *Tetrahedron Lett.,* 1984, **25**, 285.

5. (a) M. Suzuki, M. Kambe, H. Tokuyama, and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2002, **41**, 4686. (b) M. Suzuki, M. Kambe, H. Tokuyama, and T. Fukuyama, *J. Org. Chem.*, 2004, **69**, 2831.
6. For a similar reaction, see: I. D. Ivanchikova, R. N. Myasnikova, and M. S. Shvartsberg, *Russian Chemical Bulletin* (Translation of *Izvestiya Akademii Nauk, Seriya Khmicheskaya*) 1998, **47**, 1975.
7. **A typical procedure for the conversion of *o*-nitrophenylacetylene derivatives to indoles by catalytic hydrogenation. Preparation of 2-*n*-butyl-*1H*-indole.** A solution of 1-hex-1-ynyl-2-nitrobenzene **5a** (4.30 g, 21.2 mmol) in pyrrolidine (35.0 mL, 423 mmol) was stirred at 80 °C for 1 h. After removal of pyrrolidine on a rotary evaporator, the residue was dissolved in EtOH (42 mL), to which was added 10% Pd/C (23 mg, 2.1 mmol). After stirring for 4 h under a hydrogen atmosphere at rt, the reaction mixture was filtered through a pad of Celite, and concentrated. The residue was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to afford 2-butyl-1*H*-indoles **8a** (3.43 g, 84%); IR (film, cm^{-1}) 3400, 3056, 2956, 2930, 2871, 2300, 2342, 1877, 1768, 1617, 1584, 1551, 1458 1415, 1341, 1286, 1232, 1150, 1013, 926, 845; ^{1}H NMR (400 MHz, $CDC1_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.36 (m, 2H), 1.63 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 6.19 (s, 1H), 7.03-7.11 (m, 2H), 7.17 (d, *J*= 9.0Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.54 (br, IH); ^{13}C NMR (100 MHz, $CDC1_3$) δ 13.8, 22.3, 27.8, 31.2, 99.3, 110.3, 119.5, 119.6, 120.8, 128.8, 135.7 140.0; HRMS calcd for $C_{12}H_{15}N$ 173.1204, found 173.1204; Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73 N, 8.08. Found: C, 83.47; H, 8.97; N, 8.02.
8. A modification of the Leimgruber-Batcho protocol for the synthesis of 5-nitroindole, see: A. Kasahara, T. Izumi, T. Kikuchi, and L. Xiao-ping, *J. Heterocycl. Chem.,* 1987, **24**, 1555.
9. K. Sonogashira, 'Coupling reactions between sp^2 and sp carbon centers,' in *Comp. Org. Synth.,* vol. 3, 521, ed. by B. M. Trost and I. Fleming, Pergamon, Oxford, 1991.
10. A review, see: Ref. 1e.
11. (a) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.,* 1986, **34**, 2362. (b) A. N. Tischler and T. J. Lanza, *Tetrahedron Lett.,* 1986, **27**, 1653. (c) T. Sakamoto, Y. Kondo, S. Iwashita, and H. Yamanaka, *Chem. Pharm. Bull.,* 1987, **35**, 1823. (d) Y. Kondo, S. Kojima, and T. Sakamoto, *J. Org. Chem.,* 1997, **62**, 6507.
12. (a) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.,* 1966, **31**, 4071. (b) J. Fujiwara, Y. Fukutani, H. Sano, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.,* 1983, **105**, 7177.
13. (a) E. C. Taylor, A. H. Katz, and H. Salgado-Zamora, *Tetrahedron Lett.,* 1985, **26**, 5963. (b) D. E. Rudisill and J. K. Stille, *J. Org. Chem.,* 1989, **54**, 5856. (c) K. Iritani, S. Matsubara, and K. Utimoto, *Tetrahedron Lett.,* 1988, **29**, 1799.