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Copper-Catalyzed Synthesis of Enantioenriched Tetraarylethanes

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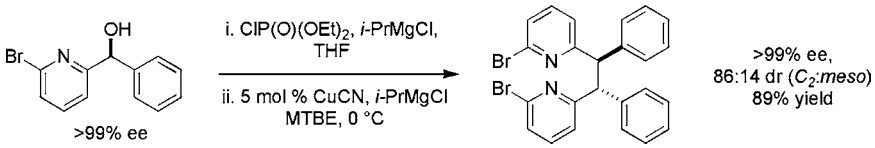
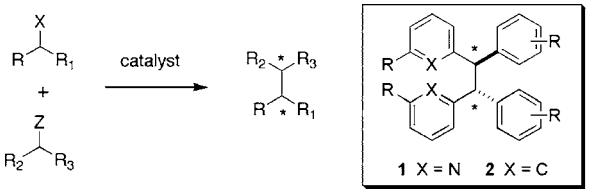
ABSTRACT



Herein we report the asymmetric synthesis of 1,2-dipyridyl-1,2-diarylethanes via an unusual Cu(I)-catalyzed dimerization reaction. Subjection of a variety of enantioenriched substituted 2-pyridyl alcohols to a one-pot protocol generates the desired products in good yields and diastereoselectivities and with ee's up to >99%.

Significant advances have been made in the field of metal-catalyzed couplings of activated and unactivated C-sp^3 alkyl halides in recent years.[1] Several notable communications detailing the metal-mediated cross-couplings of primary alkyl and benzylic C-sp^3 electrophiles in Negishi, Kumada, Stille, Hiyama, and Suzuki−Miyaura reactions have significantly advanced the field.[1,2] Although efforts have been focused largely on reactions involving primary C-sp^3 electrophiles, there have also been noteworthy achievements utilizing secondary alkyl halides. Fu has demonstrated that secondary C-sp^3 electrophiles can be used in nickel-mediated cross-coupling reactions with alkyl Zn and Si nucleophiles;[3] of particular note is the example of asymmetric Negishi cross-couplings of secondary α-bromoamides.[3a] Despite these seminal contributions, to our knowledge, there are no examples in the literature of metal-catalyzed couplings of C-sp^3 secondary alkyl groups to generate vicinal C-sp^3 chiral centers in a stereodefined manner (eq 1). Herein we report the enantioselective synthesis of 1,1,2,2-tetraarylethanes (**1** and **2**) which employs an unusual copper-catalyzed dimerization of enantioenriched aryl−heteroaromatic secondary phosphonates. To our knowledge, this is the first reported method for generating these potentially interesting medicinal and ligand scaffolds in an enantioselective manner.[4]



(1)

During the course of our studies toward the synthesis of a medicinal target, we began studying the feasibility of displacing dibenzylic phosphonate ester **3** with isopropyl magnesium chloride to generate **4** (eq 2). To our surprise, subjection of racemic **3** to 5 mol % of CuCN and *i*-PrMgCl at room temperature produced none of the desired product;

(1) For a recent review, see: Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688.

(2) Benzylic phosphonates/halides: (a) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198−9202. (b) Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871−2873. (c) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875−4878. (d) Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121−4124. (e) Nobre, S.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225−8228. Allylic phosphonates: (f) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689−690. (g) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017−6028. Alkyl halides: (h) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207−2213. (i) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100.

(3) (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 4594−4595. (b) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc*. **2004**, *126*, 7788−7789. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726−14727. (d) Bonzalex-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc*. **2006**, *128*, 5360−5361. (e) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556−3558.

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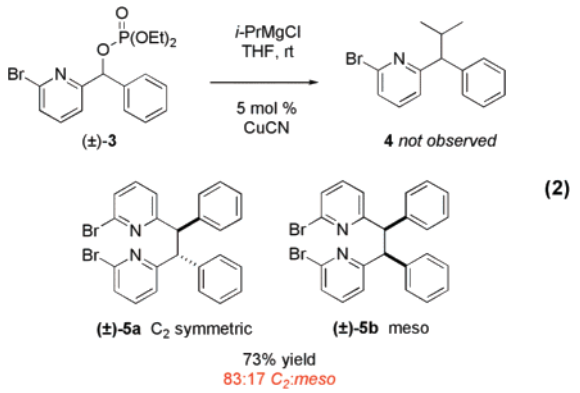
instead dipyridyl diarylethane **5** was isolated as a mixture of diastereomers (83:17 **5a**:**5b**) in 73% yield. Of particular note was the unexpectedly high preference for the formation of the C_2-symmetric diastereomer **5a** over the *meso*-**5b** isomer.



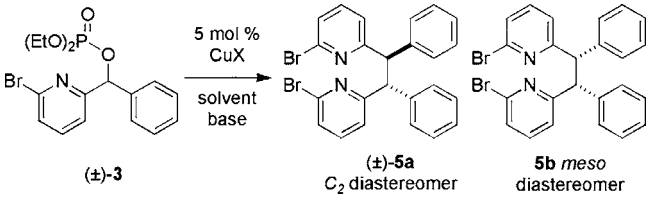
(2)

Given the unexpected nature of this product, a variety of reaction conditions were examined to optimize its yield and diastereoselectivity (Table 1). The reactions were typically run with 2.0 equiv of base; lower amounts would generally lead to incomplete conversion. Several other bases were examined (entries 4−8), although none were as effective as *i*-PrMgCl. An improved yield and modest improvement in dr was observed when MTBE was used as a solvent instead of THF (entry 10, 84% yield). Alternative copper sources were examined (entries 11 and 12) and found to be effective catalysts for the dimerization; however, CuCN consistently provided superior results. It is interesting to note that both Cu(I) or Cu(II) salts provided competent catalysts (entry 11); however, when the reaction was performed in the absence of copper (entry 13), no product was observed, thus highlighting the importance of the presence of catalytic copper in this reaction.

With optimized conditions in hand, we sought to examine the effect of the activating group on the dimerization process. As Table 2 illustrates, substrates containing a variety of leaving groups were prepared and assessed with respect to their ability to participate in the dimerization. Chloride **6** provided a nearly equivalent result to that observed with phosphonate **3**. Although bromide **7** and mesylate **8** provided the desired product, the yields were significantly diminished, largely due to the formation of side products. Tosylate **9** and trifluoroacetate **10** both failed to generate **5**; the former reaction produced a complex mixture of products, and the latter hydrolyzed quickly to the alcohol under reaction conditions. Although both chloride **6** and phosphonate **3** were viable substrates, the phosphonate ester was chosen for the study of the asymmetric dimerization due to its ease of synthesis in optically enriched form.

Having developed an optimized method for the synthesis of C_2-symmetric 1,1,2,2-tetraaromatic ethanes from benzhydryl phosphonates, we turned our attention to the enantioselective synthesis of **5a** to determine whether the integrity of the stereogenic center would survive the dimerization process. Chiral alcohol (−)-**12** was obtained in >99% ee via a biocatalytic asymmetric reduction of the corresponding ketone **11** using a commercially available ketoreductase (KRED19) and a subsequent recrystallization. Alcohol (−)-**12** was then subjected to $ClP(O)(OEt)_2$ and *i*-PrMgCl to generate phosphonate ester **3** in 96% isolated yield (Scheme 1). When **3** was subjected to our optimized

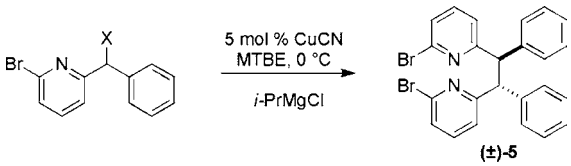
Table 1. Reaction Optimization



entry	CuX/solvent	base/temp	% yield (C_2 + *meso*)	dr[a] (C_2:*meso*)
1	CuCN/THF	*i*-PrMgCl, rt	73	83:17
2	CuCN/THF	*i*-PrMgCl, 0 °C	74	85:15
3	CuCN/THF	*i*-PrMgCl, −40 °C	0	
4	CuCN/THF	PhMgCl, 0 °C	<5	
5	CuCN/THF	MeMgCl, 0 °C	11	85:15
6	CuCN/THF	*t*-BuMgCl, 0 °C	28	85:15
7	CuCN/THF	MeLi or PhLi, 0 °C	0	
8	CuCN/THF	Et_2Zn, 0 °C	0	
9	CuCN/Et_2O	*i*-PrMgCl, 0 °C	78	87:13
10	CuCN/MTBE	*i*-PrMgCl, 0 °C	84	88:12
11	CuI/MTBE	*i*-PrMgCl, 0 °C	79	87:13
12	Cu(OTf)$_2$/MTBE	*i*-PrMgCl, 0 °C	60	85:15
13	no Cu/MTBE	*i*-PrMgCl, 0 °C	0	

[a] Diastereomeric ratio was determined by HPLC.

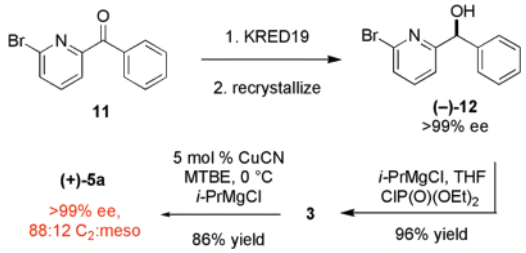
Table 2. Study of Various Leaving Groups



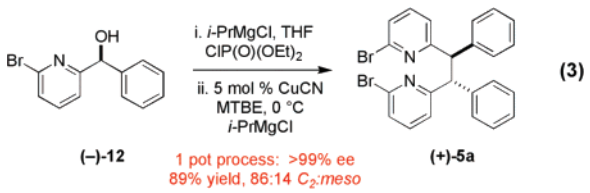
entry	X	% yield (C_2 + *meso*)	dr (C_2:*meso*)
1	OP(O)(OEt)$_2$ (**3**)	84	88:12
2	Cl (**6**)	83	88:12
3	Br (**7**)	43	62:38
4	OMs (**8**)	28	78:22
5	OTs (**9**)	0	
6	$OCOCF_3$ (**10**)	0	

(4) Alternative methods for accessing racemic tetraarylethanes: (a) Khurana, J. M.; Chauhan, S.; Maikap, G. C. *Org. Biomol. Chem.* **2003**, *1*, 1737−1740. (b) Habibi, M. H.; Farhadi, S. *Tetrahedron Lett.* **1999**, *40*, 2821−2824. (c) Li, Y.; Izumi, T. *Synth. Commun.* **2003**, *33*, 3583−3588. (d) Schlogl, K.; Weissensteiner, W. *Synthesis* **1982**, 50−53. (e) Ymada, Y.; Momose, D. *Chem. Lett.* **1981**, 1277−1278. (f) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658−8659. (g) Canty, A. J.; Minchin, N. J. *Inorg. Chim. Acta* **1985**, *100*, L13−L14. (h) Canty, A. J.; Minchin, N. J. *Aust. J. Chem.* **1986**, *39*, 1063−1069. (i) Skattebol, L.; Boulette, B. J. *Organomet. Chem.* **1970**, *24*, 547−548. (j) Newkome, G. R.; Roper, J. M. *J. Org. Chem.* **1979**, *44*, 502−505.

Scheme 1. Asymmetric Two-Pot Dimerization



dimerizationconditions, we were delighted to observe a yield and diastereoselectivity comparable to that obtained with (±)-**3** (86% yield, 88:12 dr); however, the C_2-symmetric product **5a** was obtained in >99% ee! Since both the phosphonate formation and dimerization involved the use *i*-PrMgCl, this reaction had the potential to be carried out as a one-pot process. Although phosphonate ester formation was low yielding in MTBE, this problem could be circumvented by carrying out the one-pot reaction in THF/MTBE to give the desired product in 89% yield, 86:14 dr, and >99% ee for **5a** (eq 3).



(3)

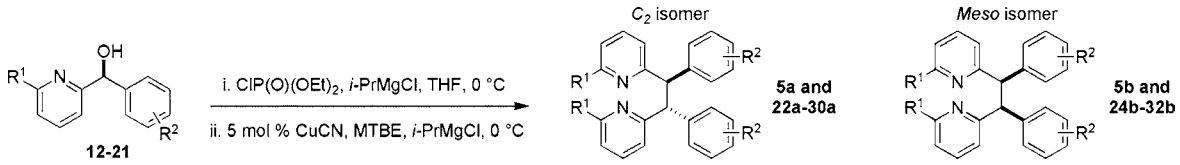
Having established conditions for the one-pot dimerization protocol, we next examined the scope of this reaction with a variety of enantioenriched chiral alcohols. Again, optically active alcohols **13**−**16**, **20**, and **21** were synthesized via an asymmetric biocatalytic reduction of the corresponding ketones. Each of the corresponding ketones was subjected to a small ketoreductase (KRED) library screen, and the optimal enzyme was chosen based on conversion and enantioselectivity.[5] The biocatalytic reductions were then scaled up, and when possible, the resulting alcohols were recrystallized to upgrade enantiomeric purity. This process consistently provided alcohols with excellent ee's (83 to >99% ee).

Each alcohol was then subjected to dimerization conditions (Table 3). Several enantioenriched 3-bromo-2-pyridyl alcohols were studied to analyze the effect of the aryl group on the dimerization (entries 2−5). Electron-deficient substrates (entries 2 and 3) retained their enantiopurity well and produced highly enantioenriched tetraarylethanes; however, the diastereoselectivities were slightly diminished relative to **12**. Although more electron-rich substrates (entries 4 and 5) generated products with good levels of diastereoselectivity, there was some erosion of enantioselectivity during the course of the reaction.

As entries 6−8 illustrate, unsubstituted pyridyl alcohols **17**−**19** were found to be completely unreactive. The importance of a 3-substituent for dimerization can be attributed to deactivation of the copper catalyst via pyridine−Cu complexation. In support of this argument, subjection of the more sterically hindered 3-methyl-2-pyridyl alcohol **20** to dimerization conditions did afford the expected dimer in 51% yield, 72:28 dr, and 50% ee. Additionally, 3-chloro-2-pyridyl alcohol **21** performed well, providing a nearly equivalent result to that observed with **12** (entry 10).

To determine if the pyridine component was mechanistically essential for dimerization, two dibenzylic alcohols were examined (Scheme 2). In the presence of 100 mol % of CuCN, benzhydrol could be dimerized to provide tetraphenylethane in 30% yield.[6] Although this reaction proceeds with

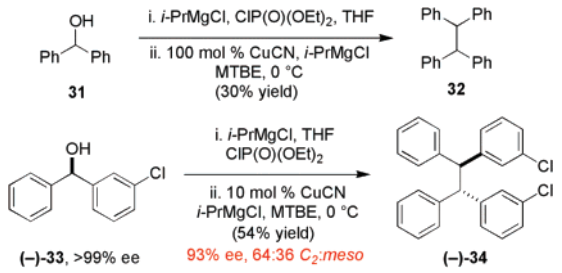
Table 3. Substrate Scope



entry	alcohol[a]	R^1	R^2	% ee of alcohol	product,[b] % yield	dr (C_2:*meso*)	% ee of product
1	**12**	Br	H	>99	**5**, 89	86:14	>99
2	**13**	Br	4-F	>99	**22**, 86	73:27	>99
3	**14**	Br	4-Cl	>99	**23**, 91	75:25	>99
4	**15**	Br	3-Me	83	**24**, 89	>95:5	44
5	**16**	Br	3-OMe	87	**25**, 80	86:14	64
6	**17**	H	H		**26**, 0		
7	**18**	H (3-pyridyl)	H		**27**, 0		
8	**19**	H (4-pyridyl)	H		**28**, 0		
9	**20**	Me	H	>99	**29**, 51	72:28	81
10	**21**	Cl	H	83	**30**, 90	85:15	83

[a] Except for **13**, absolute stereochemistry of alcohols is unknown. [b] Only relative stereochemistry shown for product.

Scheme 2. One-Pot Dimerizations of Dibenzylic Alcohols



only modest efficiency, this confirms that the pyridine moiety is not essential for this reaction to proceed. The presence of the pyridine functional group does, however, significantly increase the efficiency of the process. A chiral dibenzylic alcohol was also examined: dimerization of **33** in the presence of catalytic CuCN generated the corresponding tetraarylethane in 54% yield. Interestingly, although the diastereoselectivity ratio was lower, there was little loss in enantiopurity in the course of this reaction (>99 to 93% ee).

To gain a better mechanistic understanding of this unusual reaction, the absolute configuration of a substrate and product was determined through single-crystal X-ray analysis. As Figure 1 illustrates, crystal structures reveal that dimerization of alcohol (*R*)-**12** leads to the formation of (1*S*,2*S*)-**5**. These results suggest that the dimerization process proceeds through

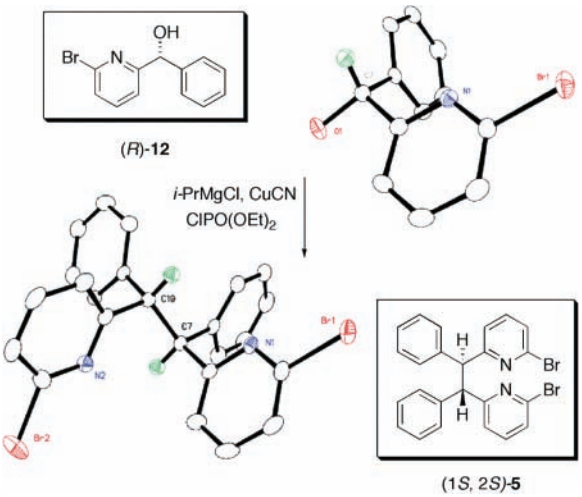


Figure 1. Absolute configuration of alcohol **12** and dimer **5**.

inversion, rather than retention, of stereochemistry at the chiral center.

It is difficult to conclusively state the mechanism of this interesting dimerization reaction;[7] however, the results presented can be collectively used to provide some insight. The absolute configuration of the substrates and products reveals that the reaction proceeds with inversion of stereochemistry and, therefore, is likely to proceed through a S_N2-type displacement of the phosphonate with a putative benzyl metal (e.g., organocopper) species.[8] It is also of particular note that the diastereoselectivities of the racemic reactions are comparable to those observed in the enantiopure reactions. This result alone implies that the dimerization process is inherently stereoselective and preferentially leads to the formation of the C_2-symmetric isomer over the *meso*-diastereomer. Studies are ongoing to elucidate the exact nature of this mechanism.

In conclusion, we have described a method for the asymmetric synthesis of tetraarylethanes via the dimerization of optically active aryl−heteroaromatic secondary alcohols. This novel method has been shown to generate a variety of products in good yields, high diastereoselectivities, and excellent enantioselectivities. This dimerization proceeds through an unusual copper-catalyzed pathway that results in the net inversion of stereochemistry, and studies are ongoing to elucidate the mechanism of this reaction.

Acknowledgment. The authors thank Robert Reamer, Adam Beard, David Pollard, and Artis Klapars (Merck Process Research) for their help and insight.

Supporting Information Available: Experimental details and spectroscopic data for new compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Truppo, M. D.; Pollard, D.; Devine, P. *Org. Lett.* **2007**, *9*, 335−338.

(6) The control reaction was run using these conditions on **31** in the presence of 1 equiv of pyridine to give **32** in 21% yield.

(7) It is well-established in the literature that Cu(I) combined with Grignard reagents forms organocuprates which can then undergo substitution reactions; for reviews, see: (a) Normant, J. F. *Synthesis* **1972**, 63−75. (b) Erdik, E. *Tetrahedron* **1984**, *40*, 641−657. Therefore, it is possible that the observed dimerization occurs through a cuprate intermediate that goes on to form the observed product. Ullman biaryl coupling reactions are also well-documented as being catalyzed by Cu(I) via either a radical or a copper insertion pathway. For recent reviews, see: (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1467. (d) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265−289.

(8) Interestingly, the reaction in which **3** was treated with preformed, stoichiometric "*i*-Pr_2CuMgCl•MgCN" (formed from 2 *i*-PrMgCl + CuCN) produced none of the desired product **5**.