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Sequential Double α-Arylation of *N*-Allylureas by Asymmetric Deprotonation and N→C Aryl Migration

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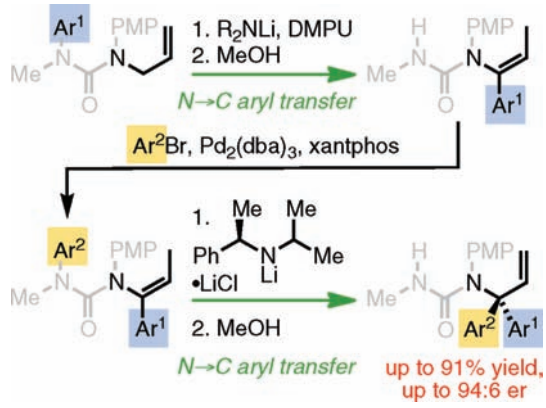
ABSTRACT



On lithiation with lithium amides, *N*-allyl-*N*′-aryl ureas undergo rearrangement with transfer of the aryl ring from N to the allylic α carbon. From the α-arylated products, a further aryl transfer under the influence of a chiral lithium amide allows the enantioselective construction of 1,1-diarylallylamine derivatives. Stereoselectivity in these reactions results from the enantioselective formation of a planar chiral allyllithium under kinetic control.

The enantioselective formation of amine derivatives bearing tertiary N-substituents is challenging,[1] and the most commonly used approaches involve addition of nucleophiles to *N*-sulfinyl ketimines[2] or reactions of lithiated *N*-acyl benzylamine derivatives.[3−5] In this paper, we report a new approach to tertiary allylamines by sequential double arylation α to nitrogen induced when *N*-allyl-*N*′-aryl ureas are deprotonated with a lithium amide base (LDA or its chiral analogues). In such cases, formation of a planar-chiral allyllithium is followed by rapid rearrangement in which C-arylation (by intramolecular N−C aryl transfer) of the allylamine results.

N-Allyl ureas **1a**−**j** were deprotonated with LDA in THF at −78 °C.[6] DMPU (1,3-dimethylpropylideneurea) was

(1) (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(2) (a) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883. (b) Cogan, D. A.; Ellman, J. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (d) Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.

(3) (a) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139. (b) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (c) Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537.

(4) For arylation α to N by rearrangement, see: (a) Clayden, J.; Dufour, J.; Grainger, D.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. (b) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567. (c) Bach, R.; Clayden, J.; Hennecke, U. *Synlett* **2009**, 421. For a review of organolithium arylation, see: O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734.

(5) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.

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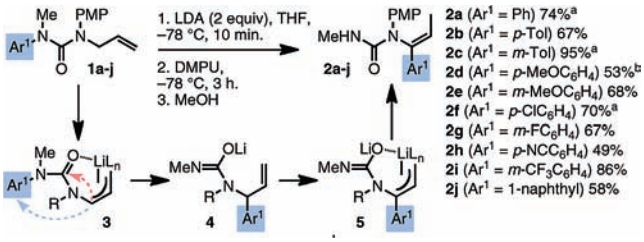
added to enhance nucleophilicity of the resulting allyllithium.[7] An orange/red color resulted, and on quenching with MeOH after 3 h at −78 °C, a product was recovered which was identified in each case as the *N*-vinyl urea **2a**−**j** (Scheme 1) in which the *N*-aryl ring had migrated to the

Scheme 1. N to C Aryl Transfer in a Lithioallyl Urea

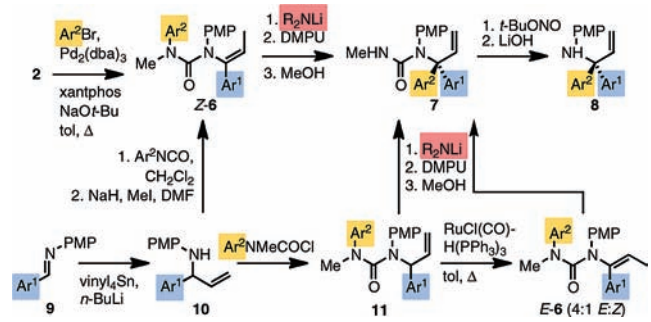


[a] Yield obtained on a 1−3 g scale. [b] Significant formation of an acyl transfer product (red arrow on **3**: see Supporting Information).

α-carbon of the allylamine. We have previously reported a related rearrangement of lithiated *N*-benzylureas,[4,5] and it appears that **2** is formed by N to C aryl transfer within the lithio derivative **3** to yield **4**, which undergoes a second lithiation (optimal yields were obtained with a full 2 equiv of LDA) to give a cinnamyllithium[8,9] species **5**. Protonation γ to nitrogen yields **2** in generally good yield, whether the migrating ring is electron deficient (**2g**,**h**,**i**) or electron-rich (**2d**,**e**). With a *p*-$MeOC_6H_4$ migrating ring, some competing attack of the allyllithium on the urea carbonyl group was observed.

It seemed likely that, given a second *N*′-aryl substituent, the cinnamyllithiums derived from **2** might also undergo rearrangement upon lithiation, introducing a second aryl ring, and hence a fully substituted stereogenic center, α to nitrogen. N-Arylation of **2a**−**c** by coupling with electron-deficient aryl bromides Ar^2Br[4b] duly yielded *Z*-**6**, which on treatment with LDA underwent rearrangement to the 1,1-diarylallylureas **7** (Scheme 2).

Scheme 2. Amines Bearing Tertiary Substituents



The amination of arenes by ureas[10] (transformation of **2** to **6**) was limited to electron-deficient coupling partners. However, the *N*′-aryl-*N*-vinyl ureas could alternatively be made straightforwardly by the other methods shown in Scheme 2. Addition of vinyllithium[11] to imine **9** gave the allylic amine **10**, which was converted to a urea and N-methylated with concomitant double bond migration to provide *Z*-**6**, presumably via the sodium *Z*-dianion.[5] *E*-**6** (4:1 *E*:*Z*) was available by formation of an allylic urea **11** using a carbamoyl chloride followed by Ru-catalyzed double bond migration.[12]

Z-Vinyl ureas **6** rearranged successfully on treatment with base (LDA) to provide allyl ureas **7** with a variety of substitution patterns and in good yield, as detailed in Table 1. Optimal yields required (a) lithiation in a coordinating solvent (other solvents gave sluggish reactions and poor yields), (b) addition of DMPU (omitting DMPU returned poorer yields), and (c) an *N*-aryl enamine starting material, which generally gave better yields than the analogous *N*-alkyl enamines. Cleavage of the urea function to give **8** from the acid-sensitive rearranged products **7** was achievable in moderate yield by nitrosation and hydrolysis,[4a] carefully avoiding exposure to acid.

Asymmetric lithiation of the achiral vinyl ureas **6** was envisaged as a suitable potential route to enantiomerically enriched amines **8**. Beak has shown that *N*-acyl allyllithiums may be deprotonated enantioselectively with alkyllithiums in the presence of (−)-sparteine,[8] and when *Z*-**6i** was treated with *s*-BuLi in the presence of (−)-sparteine in cumene at −40 °C, the product (*S*)-**7i**[13] was obtained in 45% yield and 20:80 er.

We found that better er's and yields of rearranged products **7** were obtained when lithiation/rearrangement conditions

(6) Attempted deprotonations with alkyllithiums led to byproducts arising from attack at the carbonyl group.

(7) We observe that DMPU commonly increases the nucleophilicity of organolithiums, particularly those stabilized by delocalization. See: (a) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397. (b) Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701. (c) Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5060. (d) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410. (e) Fournier, A. M.; Brown, R. A.; Farnaby, W.; Miyatake-Ondozabal, H.; Clayden, J. *Org. Lett.* **2010**, *12*, 2222.

(8) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522. Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522. Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 299. Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. Pippel, D. J.; Weisenberger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, 711. Whisler, M. C.; Beak, P. *J. Org. Chem.* **2003**, *68*, 1207. Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376.

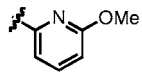
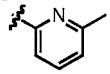
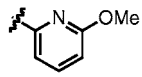
(9) Our representations of the structure of the allyllithium species **3**, **5**, and **14** are based on the structural work of Beak et al. (ref 8): their known preference for the *Z* geometry is presumably due to intramolecular Li−O coordination. N-Substituted allylithiums typically protonate in the γ-position but react with other electrophiles to give diverse mixtures of α- and γ-functionalized products. See: Gawley, R. E.; Coldham, I. In *Chemistry of Organolithium Compounds*; Rappoport and Marek, Eds.; Wiley: New York, 2004; pp 997−1053.

(10) For examples of amination reactions with ureas, see ref 4b and references therein.

(11) Tomiuka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095.

(12) Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszczynska-Sajda, K.; Kubicki, M.; Borowiak, T. *Tetrahedron Lett.* **2001**, *42*, 7095. Krompiec, S.; Pigulla, M.; Kuznik, N.; Krompiec, M.; Marciniec, B.; Chadyniak, D.; Kasperczyk, J. *J. Mol. Catal. A: Chem.* **2005**, *225*, 91.

Table 1. Synthesis and Rearrangements of Ureas *Z*-**6** with LDA

6, yield(%)(from)	Ar^1 =	Ar^2 =	product, yield (%)
Z-**6a**, 44 (**2a**)	Ph	*m*-CNC_6H_4	**7a**, 60
Z-**6b**, 71 (**2a**)	Ph	*p*-CNC_6H_4	**7b**, 75, 0[c] **8b**, 37[a]
Z-**6c**, 89 (**2a**)	Ph		**7c**, 72 **8c**, 62[b]
Z-**6d**, 72 (**2b**	*p*-Tol	*p*-CNC_6H_4	**7d**, 82
Z-**6e**, 85 (**2b**)	*p*-Tol		**7e**, 88
Z-**6f**, 70 (**2f**)	*p*-ClC_6H_4	*p*-CNC_6H_4	**7f**, 74 **8f**, 43[a]
Z-**6g**, 81 (**2f**)	*p*-ClC_6H_4		**7g**, 50[d] **8g**, 86[b]
Z-**6h**, 75 (**10a**)	Ph	Ph	**7h**, 86, 63[c], 56[e]
Z-**6i**, 75 (**10a**)	Ph	*p*-ClC_6H_4	**7i**, 86
Z-**6j**, 94 (**10a**)	Ph	*m*-FC_6H_4	**7j**, 89
Z-**6k**, 89 (**10a**)	Ph	*m*-$OMeC_6H_4$	**7k**, 56, 59[c]
Z-**6l**, 55 (**10b**)	*p*-ClC_6H_4	Ph	**7i**, 87[d]

[a] Yield of deprotection. [b] Attempted deprotection led to cyclization of the urea onto the pyridine ring in the yields quoted: see Supporting Information. [c] *N*-Methyl (instead of *N*-PMP) analogue of the substrate. [d] Reaction carried out at −60 °C; SM remained after 3 h at −78 °C. [e] No DMPU added.

similar to those in Scheme 2 were used, but with LDA replaced by a *chiral lithium amide*.[14] Both enantiomers of a range of suitable chiral amines **12·H** and **13·H** or their readily handled hydrochloride salts are available commercially or in a few steps from inexpensive starting materials. In a preliminary screen, we treated *Z*-**6b** with a series of lithium amides **12·Li** or **13·Li** in THF, adding DMPU to promote rearrangement, and the results are shown in Table 2. Formation of the lithium amides directly from the ammonium salts **12·HCl** or **13·HCl** rather than from the free bases turned out to be preferable—presumably a selectivity-enhancing effect of the resulting LiCl.[15] We found that the lithium salt of *N*-isopropyl-α-methylbenzylamine **12a·Li** performed best among the bases tried, yielding the product ureas **7** in up to 93:7 er at −78 °C.

On optimizing the choice of solvent with **12a·Li**, we found that while THF was essential for reactivity improved yields and er's were obtained when this base was used *without* DMPU, provided LiCl was present. Applying this optimal combination of base and conditions to a range of starting ureas *Z*-**6** gave further enantioselective rearrangements with selectivities lying between 84:16 and 92:8 er (Scheme 3).

We deduced the overall sense of asymmetric induction in the rearrangement by single-crystal X-ray analysis of **7f** formed with (*R*)-**12a** (Figure 1) and precipitated from chloroform; this was greatly assisted by the incorporation of two molecules of chloroform in the unit cell, and with the Flack parameter having a value of 0.0525 and an esd 0.1691, we can assign unequivocal *S* stereochemistry to this product (Scheme 3).[16] The same stereochemical course is proposed for other rearrangements promoted by (*R*)-**12·Li** and (*R,R*)-**13·Li**.

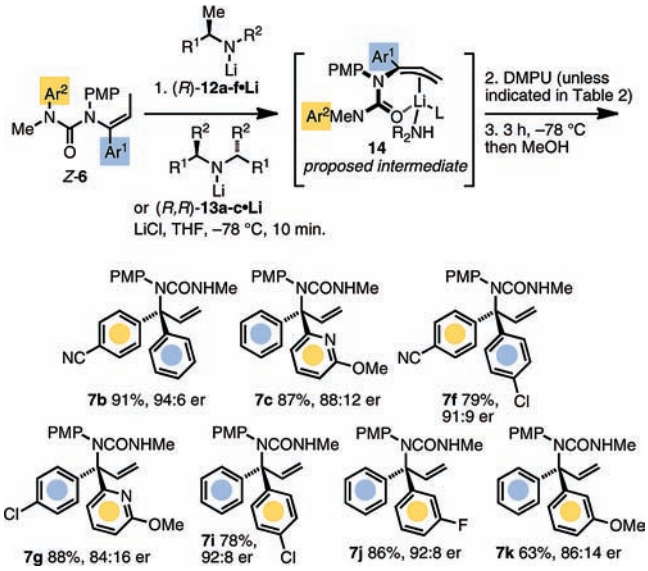
We assume, following previous related reactions,[4a,5,7d,e] that these rearrangements occur by intramolecular attack of the allyllithium on the distal aryl ring of the urea. Stereochemically, two extreme mechanistic possibilities present themselves:[17] either the stereochemistry of the product is determined by stereospecific rearrangement of a configurationally stable planar chiral allyllithium **11** or it is the result of a stereoselective reaction of configurationally unstable **11** under the kinetic or thermodynamic control of the associated chiral amine **12a**. To distinguish between these alternatives, we used **12a·Li** to rearrange the allyl urea (±)-**11** (Ar^1 =

Table 2. Enantioselectivity in the Lithiation and Rearrangement of **6**

starting material	product	Ar^1	Ar^2	base	R^1	R^2	yield (%)	er (**7**:*ent*-**7**)
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12a**[a]	Ph	*i*-Pr	63[b]	8:92[a,b]
							72	8:92[a]
							—[c,d]	11:89[a,c]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12b**[a]	Ph	*c*Hx	71	10:90[a]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12c**[a,e]	Ph	Bn	—[d]	21:79[a]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12d**[a,e]	Ph	Me	—[d]	36:64[a]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12e**[a]	1-Np	*i*-Pr	66	22:78[a]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12f**[a]	2-Np	*i*-Pr	58	8:92[a]
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**13a**	Ph	Me	72	83:17
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**13b**	1-Np	Me	—[d]	65:35
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**13c**[e]	Ph	$(CH_2)_2$	—[d]	72:28
Z-**6b**	**7b**	Ph	*p*-NCC_6H_4	**12a**[a,f]	Ph	*i*-Pr	91	6:94[a]
							—[d,g]	29:71[a]
Z-**6c**	**7c**	Ph	6-MeOPy	**12a**[f]	Ph	*i*-Pr	87	88:12
Z-**6f**	**7f**	*p*-ClC_6H_4	*p*-NCC_6H_4	**12a**[a,f]	Ph	*i*-Pr	79	9:91[a]
Z-**6f**	**7f**	*p*-ClC_6H_4	*p*-NCC_6H_4	**12a**[e,f]	Ph	*i*-Pr	54	88:12
Z-**6g**	**7g**	*p*-ClC_6H_4	6-MeOPy	**12a**[f]	Ph	*i*-Pr	88	84:16
Z-**6i**	**7i**	Ph	*p*-ClC_6H_4	**12a**[f]	Ph	*i*-Pr	78	92:8
							—[c,d]	87:13[c]
Z-**6j**	**7j**	Ph	*m*-FC_6H_4	**12a**[f]	Ph	*i*-Pr	86	92:8
Z-**6k**	**7k**	Ph	*m*-$MeOC_6H_4$	**12a**[f]	Ph	*i*-Pr	63	86:14
(±)-**14**	**7b**	Ph	*p*-NCC_6H_4	**12a**[f]	Ph	*i*-Pr	—[d]	50:50[h]
E-**6b**[i]	**7b**	Ph	*p*-NCC_6H_4	**12a**[f]	Ph	*i*-Pr	21[j]	73:27[j]
							41[k]	64:36[k]

[a] (*S*)- or (*S,S*)-enantiomer of base used. [b] At −90 °C. [c] At −60 °C. [d] Not isolated: complete conversion to product by NMR. [e] LiCl not present. [f] Without DMPU. [g] Et_2O as solvent: no reaction was observed in cumene, and in toluene a very slow reaction gave 58:42 er. [h] Also (±) with 0.5 equiv of base. [i] 4:1 mixture of *E* and *Z* isomers. [j] After 30 min. [k] After 60 min.

Scheme 3. Asymmetric Lithiation−Arylation



Ph; $Ar^2 = p\text{-}NCC_6H_4$). Complete conversion to racemic **7b** was observed (Table 2), despite the equivalence of allyllithiums formed from *Z*-**6b** and (±)-**11**. The stereochemistry of the product is therefore determined by stereoselective *formation* of the allyllithium and not its stereoselective *reaction*.

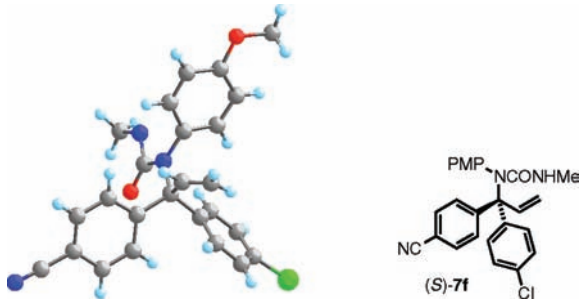


Figure 1. X-ray crystal structure of (*S*)-**7f** (formed with (*R*)-**12a**).

Racemic product was also formed slowly from *E*-**6b** (Table 2): rapid formation of a low (<25%) yield of enantiomerically enriched **7b** was observed from a 4:1 mixture of *E*- and *Z*-**6b**, followed by a slower increase in yield and erosion of product er.[18] Enantioselective formation of an organolithium by a chiral lithium amide other than by asymmetric deprotonation of one of a pair of enantiotopic protons is apparently unprecedented.[14]

The allyl urea products **7** are potentially intermediates for the synthesis of allyl amines or, after oxidation, difficult to obtain 1,1-diaryl α-amino acids. We are currently exploring further applications of these versatile amine derivatives in synthesis.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. Crystallographic data for **7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Stereochemistry was deduced from the identity of the enantiomer of **7i** given both by *s*-BuLi-(−)-sparteine and by (*S*)-**12a**. It is not clear however how this relates to the stereochemistry of the lithiated intermediate formed by enantioselective deprotonation (ref 8) or whether the subsequent rearrangement is stereochemically retentive (refs 4a, 5) or invertive (refs 7d, e).

(14) For an overview of the chemistry of chiral lithium amides, see: (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (b) Simpkins, N.; Weller, M. D. *Topics in Stereochemistry*; Gawley, R., Ed.; 2010; Vol. 26, p 1. (c) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38. For a related asymmetric deprotonation of a carbamate, see: (d) Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R.; Hoppe, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 1423.

(15) For a discussion of the beneficial effect of LiCl on many organolithium reactions, see: Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231, and references therein.

(16) The X-ray crystal data for **7f** have been deposited with the Cambridge Crystallographic Data Centre, deposition number 777622.

(17) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.

(18) The results from the 4:1 mixture of *E*- and *Z*-**6b** are consistent with the rapid, enantioselective lithiation and rearrangement of *Z*-**6b** followed by slow, racemic lithiation and rearrangement of *E*-**6b**.